Incidence and Risk Factors of Open-Angle Glaucoma

The Rotterdam Study

Simone de Voogd

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Incidence and Risk Factors of Open-Angle Glaucoma

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Contents

Publications and manuscripts based on the studies described in this thesis

Chapter 2

De Voogd S, Skenduli-Bala E, Wolfs RCW, Van Leeuwen R, Ikram MK, Jonas JB, Bakker D, Hofman A, De Jong PTVM. Causes of incident visual field loss in a general elderly population: the Rotterdam Study.
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Chapter 3

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Ophthalmology. 2005; 112: 1487-1493.

Chapter 4

Ikram MK, De Voogd S, Wolfs RCW, Hofman A, Breteler MMB, Hubbard LD, De Jong PTVM. Retinal vessel diameters and incident open-angle glaucoma and optic disc changes: the Rotterdam Study.
Invest Ophthalmol Vis Sci. 2005; 46: 1182-1187.

Chapter 5

De Voogd S, Ikram MK, Wolfs RCW, Jansonius NM, Witteman JCM, Hofman A, De Jong PTVM. Is diabetes mellitus a risk factor for open-angle glaucoma? The Rotterdam Study.
Ophthalmology. Provisionally accepted.

Chapter 6

De Voogd S, Wolfs RCW, Jansonius NM, Witteman JCM, Hofman A, De Jong PTVM. Atherosclerosis, C-reactive protein, and risk of open-angle glaucoma. The Rotterdam Study.
Invest Ophthalmol Vis Sci. Provisionally accepted.

Chapter 7

De Voogd S, Wolfs RCW, Jansonius NM, Uitterlinden AG, Pols HAP, Hofman A, De Jong PTVM. Polymorphisms of estrogen receptor alpha and beta and risk of open-angle glaucoma. The Rotterdam Study.
Submitted.

1

INTRODUCTION

Introduction

Glaucoma is one of the poorest understood and defined eye diseases among those known since our era. Despite two millennia of writing about glaucoma, a straightforward and clear-cut definition is not available worldwide. In essence, glaucoma is an eye disease characterized by loss of retinal ganglion cells and their axons. Clinically, this loss becomes apparent by cupping, also called excavation, of the optic disc and concomitant visual field loss. There are many subgroups of glaucoma, separated by causes, genetics, or morphology, and within each group there may be tens of different glaucoma types. From the start, I would like to point out that this thesis focuses on primary open-angle glaucoma. This is glaucoma in which the persons have open angles in their anterior eye chamber, through which the intraocular fluid leaves the eye. Moreover, all causes of secondary glaucoma, such as inflammation, medication, and systemic disorders, should have been eliminated with a reasonable amount of certainty. Since open-angle glaucoma cases with pseudoexfoliation were not specifically excluded at baseline of the Rotterdam study, we prefer to refer to open-angle glaucoma instead of primary open-angle glaucoma although during follow-up, no pseudoexfoliation was observed.

Haffmans and Donders in 1862 were the first to point out that open-angle glaucoma could be present without signs of inflammation. Donders also was the first to measure the intraocular pressure (IOP) in a routine way on his patients.[1]

Equipment to measure the IOP gradually improved and until the 1970s open-angle glaucoma was considered only to be present when the IOP rose above 21 mmHg. During the past decades, a shift in the definition of open-angle glaucoma occurred. The specific, abnormal configuration of the optic disc and the concomitant visual field defects became more important for the diagnosis whereas the IOP was no longer a pathognomonic sign for open-angle glaucoma. Glaucoma was, rather arbitrary, divided into two groups: high-tension glaucoma and normal tension glaucoma.[2, 3] The exact role of the IOP remained nonetheless subject for debate. Were there now two separate disease entities or was IOP only a risk factor? The discussion was based on the observations that not all persons with an elevated IOP developed optic disc damage and visual field loss, and on the other hand that some persons developed optic disc excavation with associated visual field loss despite normal IOP.[4-6] The former are now called persons with ocular hypertension and the latter people with low-tension glaucoma.[7] Thus there is still a large variety in definitions of open-angle glaucoma.[8-10]

Of late, some authors define open-angle glaucoma only on certain optic disc characteristics.[11, 12] Due to development of equipment and software for evaluating the optic disc and the retinal nerve fiber layer, detection of early changes in the optic disc is now more reliable. Previously, we only evaluated the optic disc by ophthalmoscopy, and considered a diagnosis of open-angle glaucoma certain when corresponding visual field loss had occurred. Nowadays, visual field loss is considered to be a late phase in the process of the development of open-angle glaucoma because a considerable amount of damage to the optic nerve fibers is already present when the first signs of visual field loss become apparent.[13-16] Intraocular pressure is now seen as a risk factor for open-angle glaucoma.[17]

By deciding which parameters should be used for diagnosing open-angle glaucoma, we have not come yet to a clear definition. One can look at the optic disc, visual fields, and IOP, but where lies the border between health and disease? A simple example is the IOP, which is measured on a continuous scale. There is not a clear cutoff point, above which open-angle glaucoma appears. In daily practice, everyone assumes that if a patient has an IOP higher than two standard deviations above the mean, e.g. higher than 21 mmHg, he or she has ocular hypertension and is at increased risk for open-angle glaucoma. In fact, persons with an IOP in the upper so-called normal range (8-21 mmHg) also have a higher risk of open-angle glaucoma than in the lower range.[18] Another problem facing the diagnostic process is the accuracy of the measurement. The IOP can be determined by air-puff or applanation tonometry, each having its advantages and disadvantages.[19, 20] The most commonly used method in ophthalmic practice is the Goldmann applanation tonometry, which measures the force needed to flatten the cornea over a certain area through direct contact with the cornea. Goldmann assumed the central corneal thickness to be 500 µm and he stressed that variation in thickness could theoretically affect the measurement.[21] Later on, it was confirmed that readings from the tonometer were influenced by the corneal thickness and rigidity.[22-24] Thicker corneas lead to higher IOPs. New devices for tonometry are being developed which take into account this corneal thickness.[25]

Evaluating optic disc parameters encounters the same difficulties as IOP measurements. The characteristic glaucomatous cupping is in fact a continuous process on a continuous scale. The cutoff point where normal cupping ends and glaucomatous cupping begins is not defined. The size of the optic disc may vary tenfold between 0.5 and 5.4 mm^2, and is an important factor in judging the amount of cupping.[26] In small optic discs it appears that glaucomatous damage occurs with

less cupping than in large ones, which already often have a large physiological cup by themselves.[27] Also, evaluating the size of the cup is more difficult in small discs. Automated measurements of the optic cup show considerable variation,[28, 29] partly due to the arbitrary distance between the retinal surface and the upper level of the cup.

Glaucomatous visual field loss is in fact a diagnosis by exclusion.[30] The different shapes of the visual field loss are cues for their causes. For example hemianopia, e.g. blindness or reduction in sensitivity in one half of the visual field, not crossing the vertical meridian, is normally caused by diseases in the higher visual pathways and not by open-angle glaucoma. Other causes for visual field loss, such as ageing macular disease or retinal vascular occlusion can be seen directly in the eye. If no other causes are detected and the pattern of the visual field loss follows the direction of the neurons in the retina, glaucomatous visual field loss is very likely.

The pathogenesis of primary open-angle glaucoma is thought to be death of retinal ganglion cells and their axons due to an apoptotic process.[31] The reasons for the apoptosis still have to be elucidated. Several theories have emerged in the literature. Four possible pathways are mechanical compression,[31-37] vascular ischemia,[38-40] excitotoxicity,[41-44] and genetic susceptibility.[45-51]

Mechanical compression causes deformation and backward bowing of the lamina cribrosa, the fibrous tissue at the bottom of the optic cup. It blocks anterograde and retrograde axonal transport in the optic nerve fibers where they pass through the lamina cribosa.[31-33] The connective tissue and extracellular matrix in the optic disc possibly change due to the influence of a relatively high IOP or a high pulse pressure.[34-37]

Vascular ischemia of the optic nerve head is often mentioned but the exact mechanism has to be further explored. The blood supply of the optic nerve head comes in general from the short posterior ciliary arteries. If the blood flow is lowered, ischemia at the optic disc can lead to death of the surrounding tissues and distort the transportation of nutrients and waste products, leading to accumulation of toxic substances and eventually to retinal ganglion cell death. Impaired autoregulatory mechanisms, low perfusion pressures, or changes in the autonomic nervous system can all result in vascular ischemia.[38-40]

Excitotoxic amino acids, such as glutamate, were found to be increased in glaucomatous eyes.[41] Glutamate is a neurotransmitter in the retinal ganglion cells, but at high levels it is a neurotoxin, resulting in retinal ganglion cell death.[42-44]

Open-angle glaucoma is genetically heterogeneous. Seven chromosomal loci have been identified: *GLC1A*, *GLC1B*, *GLC1C*, *GLC1D*, *GLC1E*, *GLC1F*, and *GLC1G* with three associated genes: myocilin (*MYOC)*, optineurin (*OPTN*), and *WDR36*.[45, 46] Several more genes are under investigation, in which some showed a relationship with open-angle glaucoma.[47-51]

To find risk factors for open-angle glaucoma and for better understanding of the possible pathophysiologic pathways, epidemiologic studies are helpful. In this thesis we have used data from the Rotterdam Study, a population-based prospective cohort study of persons aged 55 years and older.[52] We have first described the incidence and causes of visual field loss (Chapter 2) and the incidence of open-angle glaucoma (Chapter 3). Next, we have investigated if retinal vessel diameters, as a marker for vascular perfusion, can predict incident open-angle glaucoma (Chapter 4). In Chapters 5 and 6, the possible role of diabetes mellitus and atherosclerosis as risk factors for open-angle glaucoma is described. In search for genetic predisposition, we mention in Chapter 7 the influence of variants in estrogen receptors on incident open-angle glaucoma. Finally, the main conclusions of this thesis in larger perspective and future directions for open-angle glaucoma research are provided in Chapter 8.

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2

Incidence and Causes of Visual Field Loss in a General Elderly Population

Abstract

Objective

To determine the incidence and causes of visual field loss (VFL) in a general elderly population.

Methods

Central visual fields of both eyes were examined with suprathreshold perimetry in 3761 persons aged 55 years and older and free of VFL at baseline from the population-based Rotterdam Study. Goldmann perimetry was performed to confirm suprathreshold VFL. Causes of incident VFL (iVFL) were assessed based on all available ophthalmologic and neurological examination data and medical records.

Results

After a mean follow-up time of 6.3 years, 175 persons developed VFL. The overall incidence rate of iVFL was 7.4 per 1000 person-years, increasing to 21.1 per 1000 person-years in those aged 80 years and older. Glaucoma was the leading cause of iVFL in all age categories. The overall incidence of glaucomatous VFL was 2.0 per 1000 person-years.

Conclusions

The incidence of all VFL increased fivefold between 55 years and 80 years of age or older. After glaucoma, stroke was the second most common cause of iVFL in persons younger than 75 years, followed by age-related macular degeneration and retinal vascular occlusive disease.

Introduction

The elderly population in the Western world is rapidly increasing. This applies also to the number of elderly who live independently. Besides low visual acuity, another limiting factor for independently living is visual field loss (VFL), which is found to be associated with impairment in daily functioning,[1] with an emphasis on worse driving performance,[2,3] frequent falls,[4] and decreased quality of life.[5] It is possible to prevent progression of VFL in some diseases by early detection of the related disease. Accurate estimates of incident VFL (iVFL) and its related causes are valuable to estimate the magnitude of the VFL problem, the likelihood of the underlying cause, and the optimal frequency of visual field (VF) examination either as screening or as part of an ophthalmologic examination, as well as for risk analyses of diseases leading to VFL, such as glaucoma. Although a few studies have provided prevalence estimates of VFL[1,2,5,6] and more studies have focused on prevalence, incidence, and causes of visual impairment,[7-13] no population-based study has yet reported iVFL and its related causes.

The aim of this report from the Rotterdam Study is to provide estimates of the overall incidence of VFL and its related causes in a general, noninstitutionalized, elderly population.

Methods

Study population

This study is part of the Rotterdam Study, a population-based, prospective cohort study of all residents aged 55 years and older in a district of the city of Rotterdam, the Netherlands. Details regarding the study design and identification of the eligible cohort have been described in previous reports.[1,14] In brief, examinations of cardiovascular, locomotor, neurological, and ophthalmologic systems were conducted at the examination center after the medical ethics committee of Erasmus Medical Center had approved the study protocol and all participants had given written informed consent, all according to the Declaration of Helsinki.

After the baseline examinations in 1990-1993, a follow-up examination was performed in 1993-1994 in which we did not include perimetry because of the expected low number of iVFL, and a second follow-up was performed in 1997-1999

that did include perimetry. This study presents the results of the examinations at the second follow-up.

Of the initial eligible cohort of 10,275 individuals, 7983 (78%) persons agreed to participate in the Rotterdam Study. The ophthalmic part started after the pilot study, and therefore there were only 6780 participants in the ophthalmologic examination. At least one suprathreshold perimetry test was performed in 6347 of the 6396 noninstitutionalized persons at baseline. Baseline VF examination identified in this group 351 participants with prevalent VFL in at least one eye on Goldmann or suprathreshold testing, leaving a cohort of 5996 noninstitutionalized participants at risk for developing iVFL. This cohort provided the study population for this study.

Visual field testing and assessment of causes

The complete ophthalmologic examination and the protocol of VF examination have been described in detail in the baseline report.[1] In brief, it included indirect ophthalmoscopy of the central and peripheral retina, stereophotography of the macular area (35° field), simultaneous stereophotography of the optic disc (20° field), and VF testing. The VF of each eye was separately examined using a 52-point suprathreshold test that covered the central 24° of the field, modified from a standard 76-point screening test (Humphrey Field Analyzer 640; Zeiss, Oberkochen, Germany). If the first test was unreliable or a reliable test showed VFL in at least one eye, a second suprathreshold test was performed on that eye on the same day. In some cases when the second test was not feasible on the same day either because the person was tired or because of a lack of time, this test was done during the participant's second visit to the center, on average three weeks later. We considered VFL to be present if the participant did not respond to the light stimulus in at least three contiguous test points or in four contiguous test points when the blind spot was included in the defect. When VFL was still present on the second suprathreshold test or the test was unreliable again, Goldmann kinetic perimetry was performed on both eyes of these participants by one of two experienced full-time perimetrists, on average three months later. The perimetrist was requested to look only at the result of the last suprathreshold screening. The VF examination protocol and the equipment were the same at baseline and at follow-up. Care was taken that the same isopters tested at baseline were also tested at follow-up. Six researchers at baseline and four of them at follow-up independently graded all Goldmann VFs. In cases of disagreement, a consensus was reached among graders regarding the presence and type of defect.

For the assessment of causes of VFL, the same ophthalmologist (P.T.V.M.deJ.) as the one at baseline plus another ophthalmologist (R.C.W.W.) independently determined whether and where VFL was to be expected based on the presence and localization of fundus signs. First they looked at macular and second at optic disc-centered stereoscopic transparencies, trying to predict if and where VFL would be found. To prevent bias, transparencies of both eyes of incident cases with VFL were examined, regardless of the presence or absence of VFL. The examiners were unaware of the outcome of the Goldmann perimetry at baseline or follow-up or the clinical data. Next, the examiners looked at the VF and checked if the location and cause they predicted agreed with the outcome of the perimetry. For cases in which fundus signs did not correspond with the VFL or no cause could be found, we used information from the ophthalmologic examination at the study center as well as ophthalmologic and neurological information from medical records from hospitals and general practitioners. All discordant outcomes were discussed between the two examiners to determine the definite cause after extra information, where possible, had been obtained. The same procedures were applied to determine presence and causes of iVFL for those cases for which we only had results from suprathreshold perimetry.

Definitions

Incident VFL was defined as the presence of a VF defect in at least one eye on Goldmann perimetry in a participant from the cohort at risk or presence of a defect of at least six contiguous points on the last reliable suprathreshold perimetry performed at follow-up in those cases for which Goldmann perimetry was indicated but not performed. The flowchart for the classification of VF defects on Goldmann perimetry and the definitions of the type of defect used at follow-up were the same as at baseline.[1, 15] Glaucomatous VFL (GVFL) was defined as VFL compatible with glaucoma, thus excluding hemianopia, quadrantanopia, and an isolated central defect, after exclusion of all other ophthalmic or neuro-ophthalmic causes. Thus, optic disc characteristics were not taken into account when the diagnosis of GVFL was made. If the cause of iVFL was a set of multiple related disorders, the initiating process was taken as the cause. In some cases, iVFL was considered to be due to separate disorders. These cases were classified as having combined mechanisms of iVFL.

Data analysis

We used univariate analyses to compare baseline characteristics of participants and nonparticipants in the follow-up examination, adjusting for age and gender when appropriate. Gender differences in iVFL cases were analyzed using logistic regression modeling, adjusted for age and follow-up time.

The age-specific incidence rates (IRs) of iVFL were obtained per 5-year age category by dividing the number of incident cases by the number of person-years of the corresponding age category. The 95% confidence intervals (CIs) of the IRs were calculated using Poisson standard errors. The number of person-years was calculated by adding each individual's contribution of follow-up time to the successive age categories. For those subjects who had Goldmann perimetry, this date was used for determination of follow-up time. Similarly, the date of the suprathreshold screening was taken for persons without a Goldmann examination. For incident cases, we assumed that the VFL started at the mid-point of the follow-up time. Consequently, their contribution to the total person-years was half their individual follow-up time. The cumulative incidence (CumI) of VFL (risk of developing VFL) over a time period (t) of 5 years, was derived from the corresponding IR using the following exponential formula[16]: $CumI_{(t)} = 1 - e^{(-IR \times t)}$.

Incidence rates of GVFL, 95% CIs, and 5-year cumulative incidence for three age categories were calculated in the same way as the overall incidence of VFL. Overall, age-specific IRs for all-cause VFL and GVFL were given per 1000 person-years. The data on the type of defects and causes of VFL were given as number of eyes and percentage of total number of eyes. We used SPSS for Windows, version 11 (SPSS Inc., Chicago, IL) for all statistical analyses.

Results

From the study population of 5996 participants, during a mean ± SD follow-up time of 6.3 ± 0.76 years, 858 participants (14.3%) died and 1337 (22.3%) refused or were unable to participate in the 1997-1999 follow-up examination. Of 3801 persons (63.4%) who participated in the ophthalmologic examination at follow-up, 40 (1.1%) did not have suprathreshold screening and were unable to undergo any VF examination mainly because of their mental or physical disabilities, and 3761 (98.9%) had perimetry performed on at least one eye. General baseline characteristics of participants and nonparticipants at follow-up examination are presented in Table 2.1.

Table 2.1 Baseline Characteristics of 5138 Persons at Risk for Incident Visual Field Loss

	Participated (n = 3761)	Declined or Unable* (n = 1377)	*P* Value†
Age, y ± SD	65.5 ± 6.6	70.6 ± 8.3	<0.001
Female, %	58	69	<0.001
Visual acuity < 0.5 in the best eye, %	0.5	2.7	0.002
History of stroke, %	1.0	2.8	0.001
Demented, %‡	0.1	2.4	<0.001

SD = standard deviation.

* Included only persons alive at follow-up.

† *P* values were obtained after adjustment for age and gender when appropriate.

‡ Criteria for dementia as previously established.[20]

Compared with the participants, nonparticipants were more often female, on average older, and had a higher prevalence of stroke, dementia, and visual acuity lower than 0.50. Of 3761 participants who had the first suprathreshold screening in at least one eye, 538 (14.3%) needed further perimetry because of either abnormal test result or unreliable perimetry. Of these, 423 (11.2%) took the second suprathreshold test, and 60 (1.6%) had Goldmann perimetry without a second suprathreshold screening mainly because this test was judged to be too difficult for them. After the second suprathreshold test, 166 participants (4.4%) needed confirmatory perimetry, and 137 (3.6%) had Goldmann examination. There were 55 persons (1.5%) who refused

Table 2.2 Incidence Rates per 1000 Person-Years and 5-Year Cumulative Incidence of Visual Field Loss

Age, y	No. of Cases	Person-Years at Risk	Incidence Rate (95% Confidence Interval)		5-y Cumulative Incidence, %
55-59	8	2139	3.7	(1.9-7.5)	1.9
60-64	19	6061	3.1	(2.0-4.9)	1.6
65-69	38	6218	6.1	(4.4-8.4)	3.0
70-74	46	4913	9.4	(7.0-12.5)	4.6
75-79	32	2938	10.9	(7.7-15.4)	5.3
≥80	32	1516	21.1	(14.9-29.8)	10.0
Total	175	23786	7.4	(6.3-8.5)	3.6

further perimetry after the first suprathreshold screening, and 29 (0.8%) who refused Goldmann perimetry after they had two suprathreshold tests.

After 23,786 person-years of follow-up, 175 individuals (240 eyes) were identified as having iVFL, of which 140 cases were detected on Goldmann perimetry; 35 cases had iVFL on suprathreshold testing but refused further perimetry. Bilateral iVFL was present in 65 participants (1.7% of our study population), of whom 36 (55.4%) were in the age category 65 to 74 years. The overall IR of iVFL in at least one eye for persons aged 55 years and older was 7.4 per 1000 person-years, increasing from 3.7 per 1000 person-years at age 55 to 59 years, to 21.1 per 1000 person-years at age 80 and older. Table 2.2 also presents age-specific IRs, and the corresponding 95% CIs, and the 5-year cumulative incidence of developing VFL for 5-year age categories. Figure 2.1 shows the 5-year cumulative incidence according to age and gender. Logistic regression showed a statistically significant difference in the IR of VFL between men and women when adjusted for age. Men overall were at a higher risk for developing iVFL compared with women (odds ratio, 1.5; 95% CI, 1.1-2.0). This was consistent for most ages.

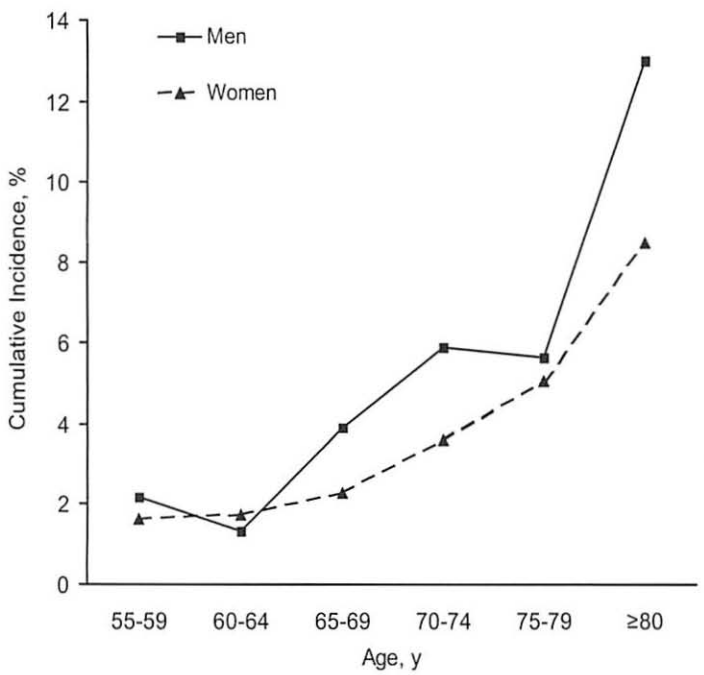

Figure 2.1
Age- and gender-specific 5-year cumulative incidence of all visual field loss.

Table 2.3 Numbers and Types of Incident Goldmann Visual Field Defects in 192 Eyes From 140 Individuals*

	Visual Field Defects per Eye, No.					
	1		2		≥3	
Defect Type†	(n = 155)		(n = 29)		(n = 8)	
Paracentral	50	(32.3)	23	(39.7)	14	(51.9)
Arcuate	30	(19.4)	19	(32.8)	5	(18.5)
Central	21	(13.5)	2	(3.4)	1	(3.7)
Quadrantanopia	20	(12.9)	1	(1.7)	0	(0.0)
Paracoecal	8	(5.2)	1	(1.7)	2	(7.4)
Hemianopic	8	(5.2)	0	(0.0)	0	(0.0)
Nasal step	7	(4.5)	1	(1.7)	0	(0.0)
Temporal-sectorial	4	(2.6)	6	(10.3)	4	(14.8)
Other‡	7	(4.5)	5	(8.6)	1	(3.7)
Total	155		58		27	

* Data are presented as number (percentage) of eyes. The 35 individuals who had only suprathreshold but no Goldmann perimetry were not included.

† Defect type is according to a slightly adapted definition of Harrington.[1, 15]

‡ Other included central residual (n=2), altitudinal (n=1), centrocoecal (n=1), temporal or nasal residual island (n=1), and undefined (n=8) defects. Undefined defect is a defect not identical to any of the other types.

For the cases with iVFL, we assessed the type of defect and causes of VFL per eye. Table 2.3 gives the type of defect(s) per eye in 140 cases, including 192 eyes with at least one defect as detected by Goldmann perimetry. The most frequent defects were paracentral scotomas, present in 32.3% of eyes with one defect and 39.7% of eyes with two defects, and arcuate scotomas, present in 19.4% of eyes with one defect and 32.8% of eyes with two defects.

Causes of iVFL per age category and per eye are shown in Table 2.4. Open-angle glaucoma (OAG) was the overall leading cause and was present in 58 eyes (24.2%), followed by stroke (n=33; 13.8%) and age-related macular degeneration (AMD) (n=28; 11.7%). Figure 2.2 presents the five most frequent causes of iVFL by age category. Among 65 cases with bilateral iVFL, 52 persons (80.0%) had the same cause of iVFL for both eyes. Stroke was the leading cause of bilateral iVFL and was present in 15 participants (28.8%), followed by OAG (n=11; 21.2%) and AMD (n=9; 17.3%). Other causes of bilateral iVFL comprised diabetic retinopathy (n=4),

Table 2.4 Causes of Incident Visual Field Loss in 240 Eyes of 175 Participants by Age*

Cause	Age, y 55-64	65-74	≥75	Overall
Open-angle glaucoma	7 (20.6)	27 (22.5)	24 (27.9)	58 (24.2)
Stroke	3 (8.8)	18 (15.0)	12 (14.0)	33 (13.8)
Age-related macular degeneration	1 (2.9)	13 (10.8)	14 (16.3)	28 (11.7)
Retinal vascular occlusion	2 (5.9)	11 (9.2)	4 (4.7)	17 (7.1)
Optic nerve head diseases other than glaucoma	5 (14.7)	6 (5.0)	4 (4.7)	15 (6.3)
Retinal disorder unspecified	3 (8.8)	9 (7.5)	3 (3.5)	15 (6.3)
Glaucoma, other types	0	4 (3.3)	5 (5.8)	9 (3.8)
Diabetic retinopathy	0	6 (5.0)	2 (2.3)	8 (3.3)
Myopia	3 (8.8)	2 (1.7)	3 (3.5)	8 (3.3)
Cataract	0	2 (1.7)	5 (5.8)	7 (2.9)
Retinal detachment	3 (8.8)	2 (1.7)	2 (2.3)	7 (2.9)
Trauma	0	3 (2.5)	2 (2.3)	5 (2.1)
Amblyopia	1 (2.9)	3 (2.5)	0	4 (1.7)
Rare causes†	4 (11.8)	5 (4.2)	3 (3.5)	12 (5.0)
Combined mechanisms‡	2 (5.9)	9 (7.5)	3 (3.5)	14 (5.8)
Total	34	120	86	240

* Data are presented as number (percentage) of eyes, both on Goldmann and suprathreshold testing.

† Rare causes comprised corneal opacities (n=2), multiple sclerosis (n=1), macular hole (n=1), macular pucker (n=1), hypertensive retinopathy (n=1), radiation retinopathy (n=1), large vitreous opacity (n=1), congenital scar (n=1), melanoma (n=1), uveitis (n=1), and central serous retinopathy with laser treatment (n=1).

‡ Combined mechanisms comprised diabetic retinopathy and anterior ischaemic optic neuropathy (n=2), diabetic retinopathy and stroke (n=1), age-related macular degeneration and anterior ischaemic optic neuropathy (n=1), age-related macular degeneration and open-angle glaucoma (n=1), myopia and open-angle glaucoma (n=1), amblyopia and open-angle glaucoma (n=1), optic disc pit and open-angle glaucoma (n=1), myopia and amblyopia (n=1), tilted disc and retinal atrophy for reasons unknown (n=1), age-related macular degeneration with myopia and open-angle glaucoma (n=1), retinal vascular occlusion and secondary glaucoma (n=2), and diabetic retinopathy and retinal vascular occlusion (n=1).

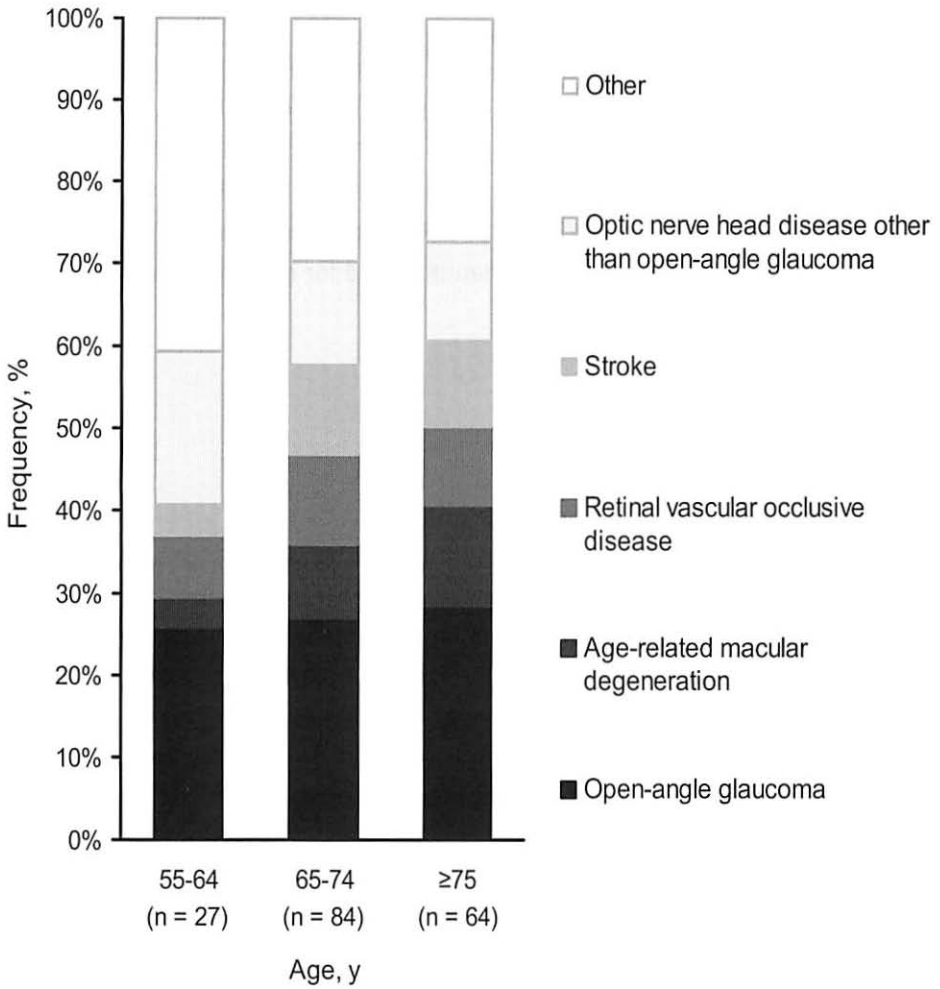

Figure 2.2

Frequency of causes of incident visual field loss in one or both eyes by age category. Numbers in parentheses are absolute numbers of persons with visual field defects in at least one eye. Relative rank may differ from Table 2.4 because frequency refers to individuals and not to eyes. The category of optic nerve head disease other than open-angle glaucoma also contains secondary glaucoma cases. Six cases had a combination of more than one of these five causes. The most plausible one was used here.

myopia (n=3), secondary glaucoma (n=3), ocular trauma (n=1), tilted disc (n=1), cataract (n=1), and unspecified retinal disorder (n=4).

We also estimated the incidence of GVFL (Table 2.5). The overall IR for participants 55 years and older was 2.0 per 1000 person-years. It increased significantly from 0.9 per 1000 person-years in age category 55 to 64 years, to 4.0 per 1000 person-years in the age category 75 years and older. Figure 2.3 shows the 5-year cumulative incidence of GVFL according to age and gender. The overall IR of GVFL seemed to be higher for men when adjusted for age (odds ratio, 1.7; 95% CI, 0.9-3.0).

Discussion

Our findings demonstrate that the overall incidence of VFL for persons aged 55 years and older increases significantly with age and is higher for men than for women. The leading cause in all age groups was OAG followed by stroke and AMD. The estimated overall IR of incident GVFL for persons aged and older was 2.0 per 1000 person-years, and the risk of developing GVFL in the next 5 years increased fivefold for persons aged 75 years and older compared with those aged 55 years. To the best of our knowledge, this is the first study providing data on the overall incidence of VFL and its causes in a general, noninstitutionalized elderly population. The relatively large study cohort ensures reliable incidence estimates for GVFL.

Before we accept our findings, we should consider the limitations and strengths of our study and analysis. Our findings relate to the Rotterdam Study cohort of participants aged 55 years and older, restricted only to noninstitutionalized subjects. No perimetry was performed at baseline or follow-up on institutionalized

Table 2.5 Incidence Rates per 1000 Person-Years and 5-Year Cumulative Incidence of Glaucomatous Visual Field Loss

Age, y	No. of Cases	Person-Years at Risk	Incidence Rate (95% Confidence Interval)	5-y Cumulative Incidence, %
55-64	7	8201	0.9 (0.4-1.8)	0.4
65-74	23	11131	2.1 (1.4-3.1)	1.0
≥75	18	4454	4.0 (2.5-6.4)	2.0
Total	48	23786	2.0 (1.5-2.7)	1.0

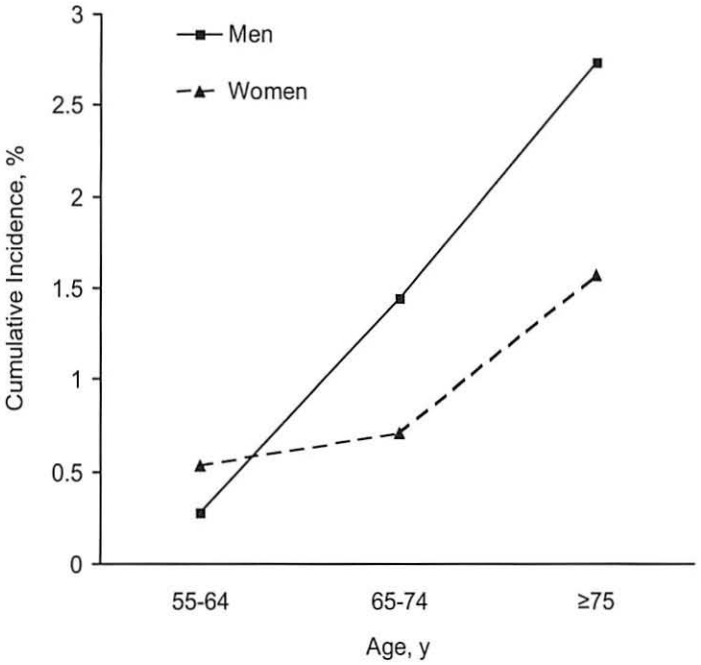

Figure 2.3
Age- and gender-specific 5-year cumulative incidence of glaucomatous visual field loss.

participants because at the start of the baseline examination they frequently had unreliable perimetry, owing to physical and mental disabilities.[1] The fact that institutionalized persons are in general older and have a higher rate of eye disorders related to cardiovascular disease than independently living individuals[17] probably led to an underestimation of iVFL in this population. Furthermore, selection bias due to the large amount of nonparticipants either refusing or unable to participate (22.3%), who were on average older and more often had a history of stroke, might further underestimate actual iVFL.

The large number of deaths among participants at risk for iVFL during the follow-up time is due to the fact that our study cohort is composed of elderly subjects. According to our findings for cause-specific iVFL, selective survival in both men and women can be an explanation for the fewer cases of iVFL related to stroke and retinal vascular occlusive disease in the age group 75 years and older. However, this was not the case for GVFL. We recently showed that there is no selective survival related to glaucoma in a general elderly population.[18] Therefore, incidence estimates of GVFL seem less biased.

A major advantage of our study is that the screening perimetry was performed on both eyes of all participants, without previous selection. Also, most persons had two suprathreshold tests before Goldmann perimetry was performed. This means that most individuals had at least four perimetric examinations (one at baseline and three at follow-up) to determine if they had iVFL. This is important because after each repeated test fewer participants retained their defect. This could be explained by a possible learning curve for the static perimetry or better comprehension of kinetic perimetry. The use of Goldmann perimetry as a confirmatory test could be considered as either a limitation or a strength. Goldmann kinetic perimetry was the gold standard when this study was designed, but recently it has been replaced with automated static perimetry. However, kinetic perimetry has more reliable results when performed on elderly people, especially those with neuro-ophthalmic disorders, because automated static perimetry can be more tiring and may lead to fixation loss. Another strength of our study is that our findings are based on a large general population cohort that was followed on average for 6.3 years. The same eye examination protocols were used at baseline and follow-up, which provided better monitoring of iVFL and its related causes and more accurate incidence estimates.

In the baseline report, we estimated the prevalence and causes of VFL. Comparing the frequency of causes of VFL at baseline with those at second follow-up, we found a slightly different distribution of causes. The leading cause in all age categories was still OAG; stroke became an important cause at follow-up, overtaking AMD and optic nerve head diseases other than OAG, which were more frequent at baseline. The higher frequency of paracentral and arcuate scotomas among cases with iVFL corresponded to OAG as the leading cause of iVFL. Our cumulative incidence of incident GVFL was lower than the 4-year risk of incident OAG in the Barbados Study.[19] This can be explained by racial influences and differences in procedures and diagnostic criteria.

Prevalence studies on VFL differed in their estimates of the overall and gender-specific prevalence, mainly owing to differences in either examination techniques or population sampling, but were consistent in showing the increase in prevalent VFL with an increase in age.[1, 2, 5, 6] The results of our study on iVFL confirm this age trend, but the paucity of other similar incidence studies prevents us from generalizing our finding that men have a higher risk of developing iVFL compared with women.

As to the implication of our findings, the estimates of the 5-year risk of developing iVFL and incident GVFL for persons 55 years and older in different age

categories can be easily applied in everyday clinical practice, although this of course becomes less reliable when the numbers become smaller.

In conclusion, our findings from this population-based study demonstrate that the incidence of all VFL increased fivefold between 55 and 80 years of age or older. Open-angle glaucoma was the leading cause in all age categories. The 5-year risk of developing incident GVFL increased fivefold for elderly people aged 75 years and older compared with those 55 years of age. Stroke was the second most common cause of iVFL before age 75 years, followed by AMD and retinal vascular occlusive disease.

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3

Incidence of Open-Angle Glaucoma in a General Elderly Population

Abstract

Purpose

To determine the incidence of open-angle glaucoma (OAG) in a general elderly white population.

Design

Population-based cohort study.

Participants

Participants 55 years and older from the Rotterdam Study, The Netherlands.

Methods

Participants at risk for incident OAG underwent at baseline (1990-1993) and follow-up (1997-1999) the same ophthalmic examination, including measurement of intraocular pressure, visual field testing, and stereo optic disc photography. The diagnosis of probable or definite OAG was made with an algorithm based on optic disc parameters and on visual field testing, independent of the intraocular pressure.

Main Outcome Measure

Five-year risk and incidence rates of OAG.

Results

In total, 3842 participants were examined (participation rate at follow-up, 78%). After a mean follow-up time of 6.5 years, probable (n=58) or definite OAG (n=29) developed in 87 persons. The 5-year risk of probable OAG was 1.2% and that of definite OAG 0.6%, and the rate rose for both together from 1% at age 60 years to approximately 3% at age 80 years. Bilateral OAG occurred five times more often after than before age 75 years. In participants with prevalent OAG in one eye, the 5-year risk of OAG in the fellow eye was five times higher than in fellow eyes of non-OAG eyes. Only 37% of the incident cases received treatment for OAG at the time of the reexamination.

Conclusions

The incidence of OAG rose significantly with age. Most of the patients with incident OAG were unaware of having OAG.

Introduction

Open-angle glaucoma (OAG) may be defined as cupping of the optic nerve head, so-called glaucomatous optic neuropathy (GON), accompanied by glaucomatous visual field loss (GVFL).[1,2] Estimates of the prevalence of OAG in population-based studies vary widely, but there is agreement that these prevalences rise steeply from 0.2 to 2.7% at age 50 to 59 years to 1.6 to 12.8% after age 80 years.[1,3-13] Although there exist various hypotheses about the causes of OAG, only a few pathophysiologic mechanisms have been elucidated. These are important because as soon as patients note visual field loss (VFL), it cannot be reversed according to present knowledge. Furthermore, the burden of OAG is expected to increase by 50% in the coming decades in Western countries.[14,15]

In contrast to numerous reports on the prevalence of OAG, there are only a few population-based studies that have presented incidence data.[16-19] Their age ranges varied from 40 years and older to between 65 to 74 years,[16-19] and local factors like racial distribution or a high prevalence of exfoliation syndrome hamper extrapolation to other populations.[20,21]

Incidence studies are important to elucidate new risk factors of OAG that may lead to the discovery of new pathophysiologic mechanisms and paradigms. They are also more suitable to estimate the cost effectiveness of screening and to calculate the optimal time interval between screenings. The aim of this study was to determine the incidence of OAG as a function of age in a general elderly white population. For comparison with similar studies, we calculated the 5-year risk of OAG. The 5-year risk (cumulative incidence) is the number of new OAG cases after 5 years of follow-up, and is further referred to in this article as incidence, unless stated otherwise. These risks were calculated using incidence rates, because we had differences in follow-up times per participant.

Methods

Study population

The ophthalmic part of the Rotterdam Study, a prospective, population-based cohort study of all residents aged 55 years and older living in a district of Rotterdam, has been described previously.[1,2] In brief, home interviews and ophthalmic examinations at the examination center were conducted after the Medical Ethics Committee of

Erasmus Medical Center had approved the study protocol and all participants had given a written informed consent, according to the Declaration of Helsinki. After the baseline examination, which took place from 1990 through 1993, follow-up examinations were performed from 1997 through 1999.

Of the initial eligible cohort of 10,275 individuals, 7983 persons (participation rate, 78%) participated in the Rotterdam Study. The ophthalmic part became operational after the screening of the randomly invited participants had started, leading to 6780 participants who underwent an ophthalmologic examination. Recalculation of the exact number of eligible participants at that point, and thus the participation rate, was not possible for logistical reasons, and thus we used the original numbers. Of these, 6773 (99.9%) participants had visual field (VF) screening, fundoscopy, optic disc photography, or a combination thereof. Baseline examination identified 221 participants with prevalent definite OAG (n=55; see Table 3.1 for definitions) or probable OAG (n=166) in at least one eye, leaving a cohort of 6552 participants at risk for incident OAG (iOAG).

Data collection

The ophthalmic examination comprised determination of the best-corrected visual acuity and Goldmann applanation intraocular pressure (IOP),[22] followed by VF screening, direct and indirect ophthalmoscopy with a 20-diopter lens, and stereoscopic fundus photography in pharmacological mydriasis.[1] The procedures were the same at baseline and at follow-up.

The VF of each eye was screened using a 52-point suprathreshold test that covered the central field with a radius of 24° (Humphrey Field Analyzer 640, Carl Zeiss Meditec Inc., Dublin, CA).[2] When the participant did not respond to the light stimulus in at least three contiguous test points (or four including the blind spot), VFL was considered to be present. If the first VF screen test was unreliable (> 33% false-positive or false-negative catch trials) or a reliable test showed VFL in at least one eye, a second suprathreshold test was performed on that eye. When VFL was still present on the second suprathreshold test, or the test was unreliable again, Goldmann kinetic perimetry was performed on both eyes of these individuals on average three months later by one of two experienced perimetrists. At follow-up, the perimetrists had access to the screening VF at follow-up but not to the baseline VFs. Screening the VF was unreliable or impossible in institutionalized persons, mainly because of physical and mental disabilities.[1] Six graders at baseline and four at follow-up independently graded all Goldmann charts for presence, type,

and depth of defect, according to a standard grading protocol.[23] Graders were masked to clinical data and optic disc appearances. Causes for VFL were sought by stereoscopically looking at macular and optic disc transparencies without additional data. In case no cause compatible with the defect(s) was seen, the results from the ophthalmic history and examination were checked. If this did not reveal a cause, information was gathered from patient files at ophthalmologist, general practitioner, and neurologist offices.[23] When this information also could not provide a cause, the VFL, after excluding hemianopia, quadrantanopia, and isolated central scotomas, was considered to be GVFL.

Simultaneous stereo color transparencies (20°) of the optic disc were digitized and analyzed with a semiautomated image analyzer (ImageNet; Topcon Optical Company, Tokyo, Japan) to obtain vertical cup-to-disc ratio (VCDR) and minimum neural rim widths.

Finally, two ophthalmologists (P.T.V.M.deJ. and R.C.W.W.) independently reviewed in a similar way once again all information on persons with a GVFL who had a VCDR < 0.6 to check possibly overlooked causes of nonglaucomatous VFL or misinterpreted VCDRs. Differences were adjudicated.

Definitions

We considered OAG to be possible only in persons who had at least in one and the same eye an open anterior chamber angle and no history or signs of angle closure or secondary glaucoma.[1] For the final diagnosis OAG, an algorithm was used based on the presence or absence of GON, GVFL, or both (Table 3.1). Cutoff values for GON were based on the 97.5th and 99.5th percentiles of the distribution in this population, preferentially on ImageNet data.[1] Minimum rim widths were not quantified by ophthalmoscopy and therefore were not taken into account in case ophthalmoscopic estimates were used. Incident OAG was defined as no or possible OAG in either eye at baseline and probable or definite OAG in at least one eye at follow-up. Excluded from this incidence definition were persons with possible GON at baseline and probable GON at follow-up because of variability in measuring GON and because a tiny increase in one of the GON criteria could lead to a change in this classification. We also did not include persons with no OAG at baseline in both eyes and possible OAG in at least one eye at follow-up in the definition of iOAG because the expected rise in prevalence of possible OAG over the different age strata failed to appear.[1]

Data analysis

We used univariate analyses of covariance to compare baseline characteristics of participants and nonparticipants in the follow-up examination, adjusted for age and gender when appropriate. Gender, age, and IOP differences in iOAG cases were analyzed using logistic regression models adjusted for age, gender, and follow-up time when appropriate.

The 5-year incidence of OAG was derived from the corresponding incidence rate using the following equation[24]: 5-year incidence = $1 - e^{(-IR \times 5)}$ (*IR* is the incidence rate and *e* is 2.718, the base of the natural logarithm).

Age-specific incidence rates per 1000 person-years of OAG were obtained for each 5-year age category by dividing the number of incident cases by the number of person-years of the corresponding age category. The number of person-years was calculated by adding each individual's contribution of follow-up time to the successive age categories. For iOAG cases, we assumed that OAG started at the midpoint of follow-up time. Differences in incidence rates between subgroups were calculated as ratios. The 95% confidence intervals (CIs) of the incidence rates and ratios were calculated using Poisson standard errors. Differences in incidence rate ratios between men and women were analysed with Poisson regression. All statistical analyses were performed using SPSS for Windows, version 11 (SPSS Inc., 2001, Chicago, IL), except for the Poisson regression, where SAS for Windows, version 8.2 (SAS Institute Inc., 2001, Cary, NC) was used.

Results

After a mean follow-up time of 6.5 years (range, 5.0–9.4 years) of the total cohort at risk (n=6552), 1244 (19%) participants were deceased and 1466 (22%) declined or were unable to participate in the follow-up examination, leaving 3842 persons (participation rate, 78%; Table 3.2). Compared with participants, nonparticipants were older and more often female and more often had a history of stroke, dementia, or a lower visual acuity. The number of participants with specific available data and the number of iOAG cases are given in Table 3.3.

There were 74 persons with a VCDR < 0.6 and a GVFL in the whole cohort (at baseline, in the follow-up phase, or both). In 37 persons we accepted the ImageNet measurements because ImageNet indicated that the data were reliable. Data of the other 37 persons were evaluated once more. In 9 persons, the baseline diagnosis

Table 3.1 Abbreviations and Definitions Used in This Article

GON (glaucomatous optic neuropathy)			
Possible GON	With	ImageNet*	VCDR ≥ 0.7 or asymmetry between both eyes ≥ 0.2 or minimum neural rim width < 0.10
	With	ophthalmoscopy*	VCDR ≥ 0.7 or asymmetry between both eyes ≥ 0.2
Probable GON	With	ImageNet	VCDR ≥ 0.8 or asymmetry between both eyes ≥ 0.3 or minimum neural rim width < 0.05
	With	ophthalmoscopy	VCDR ≥ 0.9 or asymmetry between both eyes ≥ 0.3
GVFL (glaucomatous visual field loss)			Visual field loss compatible with glaucoma (thus excluding hemianopia, quadrantanopia, and an isolated central defect) after exclusion of all possible causes, after a (neuro-) ophthalmic examination. No optic disc criteria or IOP data were used for diagnosing GVFL.
IOP (intraocular pressure)			The median of three Goldmann applanation measurements
OAG (open-angle glaucoma)			
Possible OAG			Presence of possible GON in absence of GVFL.
Probable OAG			Presence of probable GON in absence of GVFL *or* presence of GVFL in absence of any GON.
Definite OAG			Presence of possible or probable GON *and* GVFL.
iOAG (incident open-angle glaucoma)			From no or possible OAG at baseline to probable or definite OAG at follow-up. Persons going from possible GON to probable GON were excluded.
VCDR (vertical cup-to-disc ratio)			

* Ophthalmoscopic data were used in case no (reliable) ImageNet data were available.

Table 3.2 Baseline Characteristics of 6552 Persons at Risk for Incident Open-Angle Glaucoma

	Status at Follow-Up		
	Participated (n = 3842)	Declined or Unable (n = 1466)	Died (n = 1244)
Age, y ± SD	65.7 ± 6.9	71.2 ± 8.7*	77.4 ± 9.1*
Female, %	58	69*	54*
History of stroke, %	1.3	3.5†	7.2*
Demented, %	0.2	3.4	15.2*
Visual acuity < 0.5 in the best eye, %	0.9	4.8	13.5*
Institutionalized, %	0.7	5.7	27.7*

SD = standard deviation.

* $P < 0.001$, adjusted for age and gender when appropriate.

† $P < 0.05$, adjusted for age and gender.

OAG changed; 4 persons returned to no OAG, and these were added to the cohort at risk. In 17 persons, a change was made in the iOAG diagnosis. Seven cases were reclassified as no iOAG, and 10 remained in the iOAG group.

Tables 3.4 and 3.5 present age-specific incidences and incidence rates. The incidence of OAG in at least one eye for participants aged 55 years and older was 1.8%, increasing significantly from 1.4% at age 55 to 59 years to 2.6% at age 80 years and older ($P < 0.001$). Logistic regression showed no difference in incidence of OAG between men and women (odds ratio (OR), 1.3; 95% CI, 0.9-2.0). The tables also suggest differences in incidence rate ratio over age between men and women, but these were not statically significant.

Of the 87 iOAG cases, 60% of the participants had been to the ophthalmologist at least once in the previous 4 years, but only 37% were diagnosed with OAG. Of the 29 definite iOAG cases, 59% received treatment for OAG, but of the 58 probable iOAG cases, this held only for 26%.

Bilateral iOAG occurred in 12 of 87 cases (14%). The incidence of bilateral OAG in persons aged 55 to 75 years was 0.1% (95% CI, 0.05-0.3) and 0.7% (95% CI, 0.3-1.5) at age 75 years and older. This difference was statistically significant ($P = 0.003$).

The risk of iOAG significantly increased by 16% per 1-mmHg increase in highest IOP of either eye (OR, 1.16; 95% CI, 1.09-1.24). Ocular hypertension at

Table 3.3 Participants with Specific Available Data and Numbers of Incident Cases*

	n	(%)
Baseline	6552	
Perimetry	6069	(93)
Optic disc data	6489	(99)
ImageNet	5874	
Funduscopy	615	
Both perimetry and optic disc data	6006	(92)
Follow-up	3842	
Perimetry	3774	(98)
Optic disc data	3703	(96)
ImageNet	3440	
Funduscopy	263	
Both perimetry and optic disc data	3635	(95)
Both perimetry and optic disc data at baseline and follow-up	3596	(94)
Number of incident cases		
Incident OAG	87	
Definite	29	
Probable	58	
GVFL	21	
GON	37	
Unilateral / bilateral incident OAG	65 / 12	
Incident OAG in fellow eye of eye with prevalent OAG	10	
No OAG to possible OAG	360	
Possible GON to probable GON	27	

GON = glaucomatous optic neuropathy; GVFL = glaucomatous visual field loss; OAG = open-angle glaucoma.

* Data available for at least one eye.

Table 3.4 Incidence Rates per 1000 Person-Years and 5-Year Incidence of Definite and Probable Open-Angle Glaucoma

Age, y	No. of Cases	Person-Years at Risk	Incidence Rate (95% Confidence Interval)		5-Year Incidence, %
Men					
55-59	2	913	2.2	(0.5-8.8)	1.1
60-64	5	2657	1.9	(0.8-4.5)	0.9
65-69	11	2852	3.9	(2.1-7.0)	1.9
70-74	11	2116	5.2	(2.9-9.4)	2.6
75-79	8	1171	6.8	(3.4-13.7)	3.4
≥80	4	607	6.6	(2.5-17.6)	3.2
Overall	41	10316	4.0	(2.9-5.4)	2.0
Women					
55-59	4	1242	3.2	(1.2-8.6)	1.6
60-64	3	3481	0.9	(0.3-2.7)	0.4
65-69	12	3496	3.4	(1.9-6.0)	1.7
70-74	13	2847	4.6	(2.7-7.9)	2.3
75-79	8	1895	4.2	(2.1-8.4)	2.1
≥80	6	1262	4.8	(2.1-10.6)	2.3
Overall	46	14223	3.2	(2.4-4.3)	1.6
Total					
55-59	6	2155	2.8	(1.3-6.2)	1.4
60-64	8	6138	1.3	(0.7-2.6)	0.6
65-69	23	6348	3.6	(2.4-5.5)	1.8
70-74	24	4963	4.8	(3.2-7.2)	2.4
75-79	16	3066	5.2	(3.2-8.5)	2.6
≥80	10	1869	5.4	(2.9-9.9)	2.6
Overall	87	24539	3.5	(2.9-4.4)	1.8

Table 3.5 Separate Incidence Rates per 1000 Person-Years and 5-Year Incidence of Definite and Probable Open-Angle Glaucoma

Age, y	Definite Open-Angle Glaucoma			Probable Open-Angle Glaucoma		
	Incidence Rate (95% Confidence Interval)		5-Year Incidence, %	Incidence Rate (95% Confidence Interval)		5-Year Incidence, %
Men						
55-59	1.1	(0.2-7.8)	0.5	1.1	(0.2-7.8)	0.5
60-64	0.8	(0.2-3.0)	0.4	1.1	(0.4-3.5)	0.6
65-69	0.4	(0.0-2.5)	0.2	3.5	(1.9-6.5)	1.7
70-74	2.8	(1.3-6.3)	1.4	2.4	(1.0-5.7)	1.2
75-79	1.7	(0.4-6.8)	0.9	5.1	(2.3-11.4)	2.5
≥80	4.9	(1.6-15.3)	2.4	1.6	(0.2-11.7	0.8
Overall	1.5	(0.9-2.4)	0.7	2.5	(1.7-3.7)	1.3
Women						
55-59	0.8	(0.1-5.7)	0.4	2.4	(0.8-7.5)	1.2
60-64	0.3	(0.0-2.0)	0.1	0.6	(0.1-2.3)	0.3
65-69	1.1	(0.4-3.0)	0.6	2.3	(1.1-4.6)	1.1
70-74	1.1	(0.3-3.3)	0.5	3.5	(1.9-6.5)	1.7
75-79	1.6	(0.5-4.9)	0.8	2.6	(1.1-6.3)	1.3
≥80	1.6	(0.4-6.3)	0.8	3.2	(1.2-8.4)	1.6
Overall	1.0	(0.6-1.7)	0.5	2.3	(1.6-3.2)	1.1
Total						
55-59	0.9	(0.2-3.7)	0.5	1.9	(0.7-4.9)	0.9
60-64	0.5	(0.2-1.5)	0.2	0.8	(0.3-2.0)	0.4
65-69	0.8	(0.3-1.9)	0.4	2.8	(1.8-4.5)	1.4
70-74	1.8	(0.9-3.5)	0.9	3.0	(1.8-5.0)	1.5
75-79	1.6	(0.7-3.9)	0.8	3.6	(2.0-6.5)	1.8
≥80	2.7	(1.1-6.4)	1.3	2.7	(1.1-6.4)	1.3
Overall	1.2	(0.8-1.7)	0.6	2.4	(1.8-3.1)	1.2

Table 3.6 Incidence Rates per 1000 Person-Years and 5-Year Incidence of Definite and Probable Open-Angle Glaucoma in Normal Fellow Eyes of Eyes with Open-Angle Glaucoma at Baseline

Age, y	No. of cases	Person-Years at Risk	Incidence Rate (95% Confidence Interval)	5-Year Incidence, %
55-74	4	377	10.6 (4.0-28.3)	5.2
≥75	6	138	43.5 (19.5-96.8)	19.5
Overall	10	515	19.4 (10.4-36.1)	9.3

baseline, defined as highest IOP of either eye > 21 mmHg per person or use of IOP-lowering treatment, gave a three times higher risk for iOAG (OR, 3.3; 95% CI, 2.0-5.5).

At baseline, 182 persons had unilateral prevalent probable or definite OAG, of which 84 surviving persons (participation rate, 66%) were reexamined at follow-up. This population was on average older ($P < 0.001$) than the population without prevalent OAG at baseline, thus more persons died before the follow-up examination took place (30% versus 19%). In this group, OAG developed in the contralateral eye in 10 persons (12%; definite OAG, 7 persons; probable OAG, 3 persons), leading to a fivefold higher risk (95% CI, 2.9-10.6) of OAG than in eyes without any probable or definite OAG in the fellow eye at baseline (Table 3.6).

Discussion

The incidence of OAG in persons aged 55 years and older increased with age. Bilateral iOAG occurred more frequently among the eldest participants. The data showed that if one eye was affected by OAG at baseline, the risk of OAG developing in the fellow eye was five times higher when compared with no OAG in either eye at baseline.

How do our results compare with other prospective incidence studies? The Barbados Eye Studies (≥ 40 years) found a 4-year incidence of 2.2% in blacks, which is higher than in our study when adjusted for the difference in risk period and age range.[16] The Visual Impairment Project (≥ 40 years) found a lower estimate (incidence of 1.1% versus our 1.8%) that seemed to be different, but after adjustment for age was quite similar.[17] Similar to higher risks were found in two other cohort

studies from Sweden of white persons when adjusted for age. In Dalby (n=1093) the 1-year incidence was 0.24% versus our 0.25%[18]; in Tierp (n=441) the incidence rate was 6.8 per 1000 person-years versus our 4.2.[19] A retrospective population-based study in Olmsted County using different diagnostic criteria estimated an incidence rate of 0.145 per 1000 person-years.[25] So as in prevalent OAG, there is considerable variation in the estimation of iOAG.

Several explanations for this variation are possible. Each study had a different age range and risk period. Differences in age range influenced the overall estimates because iOAG occurred more frequently at a higher age. While comparing studies, one should adjust for the differences in age, and when incidence is used, one also should adjust for the duration of the risk period. However, this was not enough to explain all differences.

Race is a second important explanation. With a higher prevalence of OAG in black populations, the incidence within the same time period will be higher, too, compared with that in white populations. Furthermore, in certain areas such as Finland, Sweden, and Iceland, a high prevalence of pseudoexfoliation syndrome is observed, which increases the risk of OAG.[21] This can influence the estimates if pseudoexfoliation glaucoma is included in the number of OAG cases. In our iOAG cases no pseudoexfoliation was detected.

The examination tools used in the several studies varied, such as use of photographs or only fundoscopy, differences in VF screening design and equipment, and preselection of persons eligible for VF screening. One study did not examine persons themselves, but relied on coded diagnoses in medical records as a detection tool.[25]

A major source of variation is the definition of OAG. A uniform definition for OAG is still not available worldwide. This led to various ways of diagnosing OAG based on only GVFL or through a combination of data, such as GVFL, optic disc characteristics, IOP, and medical history. Another major complicating factor is the final judgment on the presence of OAG. This could be carried out by one principal investigator,[5] a coordinating center using an algorithm,[16] a consensus panel,[17] or by independently classifying staff members.[18] We chose predefined cutoff points and used an algorithm to come to a diagnosis in combination with a consensus panel. Because we wondered, according to present paradigms, if a small VCDR in a normal-sized disc could lead to OAG, we checked again on those OAG eyes with a VCDR < 0.6. Another issue when comparing studies regarding the diagnosis is the used definition: definite only, or combined with less certain diagnoses.

Regarding the definition of OAG, we think it is best to try to obtain the diagnosis in an objective and repeatable way to make comparison between studies on OAG possible. We have tried to accomplish this by using separate protocols for grading VFs, automated measurements for optic disc characteristics, statistically instead of intuitively determined cutoff points for VCDR and minimum rim width, and an algorithm for the diagnosis OAG.

The strength of our study is the design: prospective, population-based, and aiming at similar data collection procedures for every participant. Our large cohort size and the use of person-years instead of persons enabled us to estimate the incidence more accurately. A limitation may be the considerable number of nonparticipants at follow-up. The large number of deaths (19%) during follow-up is because our cohort was composed of elderly participants. This could lead to bias, but we have shown that there is no selective survival related to glaucoma.[26] Bias could have played a role in persons (22%) who declined follow-up examinations. They were, in general, older and more often female. During the follow-up period, a larger proportion became institutionalized. These factors can lead to an underestimation of the incidence because OAG more frequently occurs at higher age, which is associated with admission to nursing homes.[27-29] Nevertheless, our participation rate at follow-up was quite high and similar to that in the Barbados and Melbourne studies.[16, 17] Intrinsic to studying such an old cohort is the fact that the very old in the nursing homes cannot go through reliable perimetry. This could have led to underestimation of the incidence because persons with possible GON without a VF test were not included as incident cases, although some of them might have had GVFL and thus definite OAG.

Another advantage of our algorithm is the independent evaluation of GVFL and GON. This is convenient in case a person cannot undergo perimetry or when the optic disc is not visible. One cannot state that a person with a VCDR of 0.9 has no OAG because (s)he was too old or confused to have a perimetric screening test. Moreover, when analyzing risk factors for OAG, it may be advantageous to be able to perform subanalyses independently for GON and GVFL before combining them. A disadvantage of this independency occurs during the search for causes of VFL when a VF is classified without using optic disc criteria. In 29 eyes of 24 persons, we thus had a GVFL without any GON according to our criteria at the time of follow-up. For these VFLs, we could not find other causes, and the shapes of the defects were compatible with OAG. Of them, 21 were finally classified as incident probable OAG.

Gender is a possible risk factor for OAG, but both Barbados Eye Studies and Visual Impairment Project could not detect a significant difference, although there was a trend for higher incidence in men.[3, 8, 16-18, 30] In contrast to our baseline finding of a significant OR of 2.1 (95% CI, 1.2-3.6) for men versus women regarding prevalent definite OAG, our OR for iOAG was nonsignificant. When we separated our iOAG cases into probable and definite, we found an increased OR of 1.6 (95% CI, 0.8-3.3) for definite OAG in men and an OR of 1.2 (95% CI, 0.7-2.0) for probable OAG in men. An explanation is that the Barbados Eye Studies,[16] Visual Impairment Project,[17] and our study separately did not have enough cases and thus lacked power to reach significance. Interestingly, the estimates of the three studies pointed in the same direction, an increased risk of OAG for men.

Since IOP is one well-known risk factor for OAG, we performed a preliminary analysis, pending a more extensive one. Increasing baseline IOP led to a higher risk of iOAG, as it did in the Barbados Eye Studies and Visual Impairment Project.

We also included people with possible OAG in the cohort at risk. This was done because it is uncertain if possible GON, the basis of diagnosis being possible OAG, is still a physiological excavation of the optic disc or an early stage of OAG. This uncertainty was partly based on the fact that the prevalence of possible OAG at baseline remained around 15% over all age strata instead of showing an expected rise with age.[1] When the incidence analyses were repeated on persons without any OAG at baseline, the incidence decreased to 1.5%. By using logistic regression, we calculated that persons with possible OAG were 1.9 (OR, 1.9; 95% CI, 1.2-3.1) times more likely to have probable or definite iOAG than healthy persons. This justifies the idea that a VCDR ≥ 0.7, or asymmetry between both eyes ≥ 0.2, or minimum rim width < 0.1, without GVFL can indicate an early stage of OAG, as has been shown earlier.[31] Nevertheless, to obtain a high specificity in our incidence definition, we excluded persons with incident possible OAG and persons going from possible GON to probable GON in our incidence definition.

At the time of the reexamination, only a minority of the iOAG cases was treated for their disease. This is comparable with the Barbados Eye Studies and Visual Impairment Project, where 50% of the cases were visiting an ophthalmologist for OAG at the time of follow-up.[16, 17] It is clear that OAG is still underdiagnosed. Screening programs, perhaps only for subpopulation with risk factors for OAG, could solve this problem, but this needs further investigation. In conclusion, our findings demonstrate an increase of the incidence of OAG with age. The chance for bilateral iOAG in persons 75 years of age and older was fivefold higher than in those aged 55

to 75 years. Normal fellow-eyes of OAG eyes had a fivefold higher risk for developing OAG compared with fellow eyes of normal eyes. Of all persons with iOAG, only one third were treated for this disease by an ophthalmologist.

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4

Retinal Vessel Diameters, Incident Open-Angle Glaucoma and Optic Disc Changes

Abstract

Purpose

It remains unclear whether reduced retinal blood flow and smaller arterioles, reported to exist in patients with open-angle glaucoma (OAG), are a cause or a consequence of ganglion cell loss. We examined whether baseline retinal vessel diameters were related to incident (i)OAG or incident optic disc changes in a population-based sample.

Methods

In the prospective population-based Rotterdam Study, baseline diameters of retinal arterioles and venules (1990-1993) were measured in digitized images of 3469 persons (aged 55 years and older) at risk for OAG. The follow-up examinations took place from 1997 to 1999. Incident OAG was based on the presence of incident glaucomatous visual field loss and/or incident glaucomatous optic neuropathy. Changes in neuroretinal rim, cup area, or vertical cup-to-disc ratio were calculated with a semiautomated image analyzer in 2782 persons.

Results

After a mean follow-up time of 6.5 years, 74 participants had iOAG. At baseline, the mean arteriolar diameter was 147.5 ± 14.2 μm (SD) and the venular, 222.9 ± 20.0 μm. Neither arteriolar diameters (odds ratio (OR) per SD decrease, 0.82; 95% confidence interval (CI), 0.66-1.03) nor venular ones (OR per SD increase, 1.20; 95% CI, 0.95-1.53) were significantly related to iOAG. Baseline retinal vessel diameters did not predict changes in the optic disc. Additional adjustment for cardiovascular risk factors did not alter these results.

Conclusions

The data show that baseline retinal vessel diameters did not influence the risk of iOAG or incident optic disc changes. These data provide no evidence for a retinal vascular role in the pathogenesis of OAG.

Introduction

Open-angle glaucoma (OAG) is characterized by progressive loss of retinal ganglion cells and their axons, resulting in glaucomatous optic neuropathy (GON), with corresponding glaucomatous visual field loss (GVFL). Despite being the second leading cause of incurable visual impairment in the Western world, little is known about the etiology of OAG.[1, 2] Age,[1] intraocular pressure (IOP),[3] myopia,[4] African origin,[5] and family history[6] are some of the factors associated with OAG.

Other possible risk factors are those related to the perfusion of the optic nerve head or the retinal ganglion cell layer.[7-9] Data concerning the relationship between vascular risk factors and OAG remain controversial,[9] as is the association between blood pressure measured at the brachial artery and prevalent OAG.[10, 11] Peripheral vascular markers may not represent local vascular abnormalities in patients with OAG. To overcome this problem, investigators have used blood flow measurements in the ophthalmic and posterior ciliary arteries in patients with OAG,[12-16] showing 10 to 20% decreased ocular blood flow compared with age-matched control subjects.[16, 17] Some of these cross-sectional and case-control studies involved a small sample of, or highly selected, clinic-based patients. To our knowledge, prospective data on the relationship between retinal vascular factors and incident (i)OAG are not available. Because of these limitations, an important etiological question remains unanswered: whether an impaired retinal circulation plays a causative role in the pathophysiology of OAG.[9]

Recently, a semiautomated system was developed to measure retinal vessel diameters.[18] We have reported that smaller arteriolar diameters are associated with higher blood pressures and larger venular diameters with atherosclerosis and inflammation.[19] We tested in the present study the hypothesis that smaller arteriolar or larger venular diameters at baseline increases the risk of iOAG in a prospective population-based cohort. Furthermore, we investigated whether these diameters were related to incident optic disc changes.

Participants and methods

Study population

The present study was part of the Rotterdam Study, a population-based, cohort study on chronic diseases in the elderly.[1, 20] A total of 7983 persons aged 55 years and older

living in a district of Rotterdam agreed to participate. Because the ophthalmic part became operational after the screening of at-random, invited participants had started, 6780 participants underwent the ophthalmic examination.[1] The study was conducted according to the Declaration of Helsinki, and the Medical Ethics Committee of the Erasmus Medical Center approved the study protocol. Written informed consent was obtained from all participants. Baseline home interviews and examinations were performed from 1990 to mid-1993. The follow-up examinations took place from mid-1997 to the end of 1999.

The ophthalmologic examination, both at baseline and follow-up, comprised Goldmann applanation IOP;[21] visual field (VF) testing; and, after pharmacological mydriasis, direct and indirect ophthalmoscopy and simultaneous stereoscopic fundus photography of the optic disc in both eyes with a telecentric fundus camera (20° field; Topcon Optical Co., Tokyo, Japan).[1]

Retinal vessel measurements

After optic disc photographs were digitized with a high-resolution scanner, the digitized image with the best quality (left or right eye) was analyzed for each participant with a semiautomated system (Retinal Analysis, Optimate, WI; Department of Ophthalmology & Visual Science, University of Wisconsin-Madison) by four trained graders masked to the endpoints.[19] We used the improved Parr-Hubbard formula to compute the summary arteriolar and venular diameters.[22] Because eyes may have a different magnification due to refractive errors, we additionally adjusted these summary vessel measures for the refraction, using Littmann's formula to obtain corrected measures.[23] The arteriolar-to-venular ratio (AVR) was taken as the ratio of the arteriolar to venular diameters.

Optic disc morphometry

The optic disc transparencies were also analyzed independently from the retinal vessel measurements with a semiautomated image-analysis system (ImageNet; Topcon Optical Co.) to calculate the areas (in square millimeters) of the optic disc, cup, and neuroretinal rim, the minimal rim width and the vertical cup-to-disc ratio (VCDR).[24] The system's hardware, its software modules and reproducibility of measurements are described elsewhere.[25-27] The same eye was taken for both the retinal vessel diameters and optic disc measurements.

Glaucoma diagnosis

We considered OAG to be present in persons who had, at least in one (and the same) eye, an open anterior chamber angle, no history or signs of angle closure or secondary glaucoma, and the presence of GON and/or GVFL.[1]

We defined GON using measurements obtained by image-analysis, whenever available.[1] Possible GON was defined as a VCDR ≥ 0.7, asymmetry between eyes ≥ 0.2, or minimum rim width < 0.10. Probable GON was defined as a VCDR ≥ 0.8, asymmetry between eyes ≥ 0.3, or minimum rim width < 0.05. When the image-analysis data were absent, funduscopic VCDR was used, leading to a slightly different definition of probable GON based on the distribution in the population: instead of VCDR ≥ 0.8, it was VCDR ≥ 0.9.[1] Minimum rim widths were not assessed funduscopically and were, in these cases, not taken into account.

The VF of each eye separately was screened with a 52-point suprathreshold test that covered the central field with a radius of 24°. If the test was unreliable, or a reliable test showed VFL in at least one eye, this test was repeated on that eye. When the second test again was unreliable, or VFL was still present, Goldmann kinetic perimetry was performed on both eyes.[28] Glaucomatous VFL was defined as VFL compatible with OAG after exclusion of all other neuro-ophthalmic causes. Definite OAG was defined as the presence of GVFL in combination with possible or probable GON. Probable OAG was either the presence of GVFL in the absence of GON or the presence of probable GON in the absence of GVFL.[1]

Incidence of OAG was defined as having no OAG in both eyes at baseline and acquiring probable or definite OAG in at least one eye at follow-up. Excluded from this incidence definition were those who had possible GON at baseline and had probable GON at follow-up, because this increase may be quite small and due to variability in measurement of GON.

Assessment of confounders

The average of two blood pressure measurements in sitting position at the right brachial artery with a random-zero sphygmomanometer was taken. Mean perfusion pressure was calculated with the following equation: ⅔ × diastolic blood pressure + ⅓ × systolic blood pressure – IOP. Nonfasting serum total cholesterol was determined by an enzymatic procedure and high-density lipoprotein (HDL) was measured similarly after precipitation of the non-HDL fraction.[29] The ratio of the total-to-HDL cholesterol was taken. Diabetes mellitus was considered present if participants reported use of antidiabetic medication or when random or post-load serum glucose level was > 11

mmol/l.[30] Intima-media thickness was measured in the common carotid arteries by ultrasonography.[31] Information on smoking (categorized as current, former or never) was obtained during the baseline home interview.

Study sample

Of the 6780 participants in the ophthalmic part of the Rotterdam Study, 6436 persons had optic disc photographs, and, in 5674 persons, fundus transparencies were gradable for retinal vessel measurements. Excluding 157 persons with prevalent OAG, 5517 participants were at risk for iOAG. During follow-up, 838 participants died. A further 1210 refused or were unable to participate at the follow-up examination, leaving 3469 participants for the current analyses.

Also, 2782 participants had gradable stereo disc transparencies taken both at baseline and follow-up in at least one (the same) eye to calculate changes in optic disc morphometry with image-analysis system (ImageNet; Topcon).

Data analyses

To assess whether participants were different from nonparticipants or those who died, mean differences were calculated for the continuous variables using analysis of covariance and odds ratios (ORs) for the categorical ones by logistic regression models. The mean differences and the ORs were adjusted for age and gender.

Odds ratios with corresponding 95% confidence intervals (CIs) for iOAG were calculated by analyzing retinal vessel diameters, both linearly (per standard deviation) and in quartiles, adjusted for age, gender, and follow-up time, and in addition for other known cardiovascular risk factors. For additional adjustments, we included those cardiovascular risk factors that we had shown to be associated with retinal vessel diameters[19] and that also have been implicated in the pathogenesis of glaucoma.[9] Although IOP is an important risk factor for glaucoma, it was not included for additional adjustment because it was not related to the retinal vessel diameters. Quartiles were selected to secure enough cases in each category.

Because, retinal vessel measurements were performed in the eye with the best-quality fundus transparency, it could happen that the vessel measurement was performed in one eye, whereas iOAG developed in the other. In these cases, vessels were measured in the eye with iOAG, for an eye-specific subanalysis.

Incident optic disc changes were defined as the difference between follow-up and baseline measurements in neuroretinal rim area, cup area, or the VCDR. Analysis of covariance models were used to compute the age- and gender-adjusted

Table 4.1 Baseline Characteristics

		Participants (n = 3469)	Nonparticipants* (n = 1210)	Adjusted Differences†‡ (95% Confidence Interval)	Died§ (n = 838)	Adjusted Differences†‖ (95% Confidence Interval)
Age, y		65.4 (6.6)	70.1 (8.2)	4.7 (4.2; 5.2)¶	75.1 (8.6)	9.8 (9.3; 10.4)¶
Female, %		57.6	67.9	1.41 (1.23; 1.63)¶	51.0	0.62 (0.52; 0.73)¶
Diabetes mellitus, %		6.5	10.2	1.38 (1.08; 1.75)¶	21.4	2.78 (2.18; 3.56)¶
Smoking, %	Current	21.9	25.6	1.68 (1.43; 1.98)¶	28.2	2.38 (1.95; 2.90)¶
	Past	45.6	38.1	0.82 (0.71; 0.95)¶	39.2	0.65 (0.54; 0.78)¶
Diastolic blood pressure, mmHg		73.6 (10.8)	74.3 (11.7)	1.6 (0.8; 2.3)¶	73.2 (12.8)	0.9 (-0.1; 1.8)
Systolic blood pressure, mmHg		135.6 (20.7)	142.0 (22.7)	3.6 (2.1; 5.0)¶	144.9 (24.3)	3.4 (1.6; 5.2)¶
Carotid intima-media thickness, mm		0.77 (0.14)	0.80 (0.15)	0.01 (0.00; 0.02)¶	0.87 (0.17)	0.04 (0.02; 0.05)¶
Serum total cholesterol, mmol/l		6.68 (1.17)	6.71 (1.19)	0.04 (-0.04; 0.12)	6.34 (1.28)	-0.17 (-0.27; -0.07)¶
Serum HDL cholesterol, mmol/l		1.36 (0.35)	1.38 (0.36)	0.01 (-0.02; 0.03)	1.28 (0.38)	-0.04 (-0.06; -0.01)¶
Intraocular pressure, mmHg		15.5 (2.97)	15.6 (3.10)	0.14 (-0.07; 0.35)	15.3 (3.21)	-0.12 (-0.38; 0.13)
Retinal arteriolar diameters, µm		147.5 (14.2)	146.8 (14.5)	0.2 (-0.8; 1.2)	144.7 (14.8)	-0.8 (-2.0; 0.4)
Retinal venular diameters, µm		222.9 (20.0)	220.8 (21.1)	0.6 (-0.7; 2.0)	219.8 (22.9)	1.4 (-0.3; 3.1)
Arteriolar-to-venular ratio		0.66 (0.06)	0.67 (0.06)	-0.001 (-0.005; 0.003)	0.66 (0.06)	-0.007 (-0.012; -0.002)¶

Presented as unadjusted means (standard deviation) or percentages. Adjusted differences are presented as mean differences for continuous and odds ratios for categorical variables with 95% confidence interval.

* Unable or refused at follow-up.

§ Persons who died before the follow-up examination.

† Age and gender adjusted if applicable.

‡ Nonparticipants versus participants.

‖ Deceased persons versus participants.

¶ Significant ($P < 0.05$) compared with participants.

mean changes in neuroretinal rim area, cup area, and VCDR for the different quartiles of retinal vessel diameters. The statistical significance level was set at a $P \leq 0.05$, and the calculations were performed with commercially available software (SPSS Windows, version 11; SPSS Inc., Chicago, IL).

Results

Table 4.1 shows the baseline characteristics of the study population. After a mean of 6.5 years of follow-up (range, 5.2-9.4) a total of 74 participants had iOAG, of whom 52 had probable and 22 definite iOAG. In persons with iOAG, the mean arteriolar diameter at baseline was 149.8 ± 14.0 µm (SD), venular 225.6 ± 17.4 µm, and AVR 0.67 ± 0.06, and in those without iOAG the mean results were 147.5 ± 14.2, 222.9 ± 20.1, and 0.66 ± 0.06, respectively. Table 4.2 shows that neither retinal arteriolar nor venular diameters nor the AVR were related to the risk of iOAG. Categorizing retinal vessel diameters into quartiles did not show a consistent trend toward a higher risk of iOAG (Table 4.3). Additional adjustments for other cardiovascular risk factors did not affect these results.

In the 74 persons with iOAG, 8 had bilateral disease. In 40 of the persons the vessel measurements had already been performed on the eye with iOAG. For an eye-specific analysis, we also measured the retinal vessels in 26 of the remaining 34 persons who had gradable images in the same eye in which iOAG was diagnosed.

Table 4.2 Odds Ratios of Incident Open-Angle Glaucoma per Standard Deviation Difference in Baseline Retinal Vessel Diameters*

	Model I‖		Model II¶	
Generalized arteriolar narrowing†	0.82	(0.66-1.03)	0.91	(0.70-1.17)
Generalized venular dilatation‡	1.20	(0.95-1.53)	1.15	(0.89-1.49)
Arteriolar-to-venular ratio§	0.98	(0.77-1.24)	1.05	(0.81-1.37)

* OR with corresponding 95% confidence interval, n=3469.

† OR per standard deviation decrease in retinal arteriolar diameters.

‡ OR per standard deviation increase in retinal venular diameters.

§ OR per standard deviation decrease in arteriolar-to-venular ratio.

‖ Adjusted for age, gender, and follow-up time.

¶ Adjusted for age, gender, follow-up time, diabetes mellitus, smoking, total-to-HDL cholesterol ratio, mean perfusion pressure, and intima-media thickness.

In these 66 cases, neither arteriolar narrowing (OR, 0.84; 95% CI, 0.66-1.07), nor venular dilatation (OR, 1.16; 95% CI, 0.92-1.48), nor AVR (OR, 0.96; 95% CI, 0.76-1.23) were related to iOAG.

The mean area of the neuroretinal rim at baseline was 1.81 ± 0.37 mm^2 (range, 0.79-3.98), the area of the cup was 0.58 ± 0.34 mm^2 (range, 0.02-2.11), and the mean VCDR was 0.49 ± 0.13 (range, 0.04-0.78). At follow-up, the mean change in area for the neuroretinal rim was 0.029 ± 0.21 mm^2, in area of the cup was 0.021 ± 0.16 mm^2, and in VCDR was 0.004 ± 0.07. Table 4.4 presents the relationship between quartiles of retinal vessel diameters and the change in these optic disc parameters. Baseline retinal vessel diameters were not related to incident optic disc changes.

Table 4.3 Odds Ratios of Incident Open-Angle Glaucoma in Quartiles of Baseline Retinal Vessel Diameters*

	Model I†	Model II‡
Retinal arteriolar diameters		
4 (largest)	1.00 (Reference)	1.00 (Reference)
3	0.72 (0.39-1.35)	0.75 (0.38-1.48)
2	0.61 (0.32-1.18)	0.69 (0.34-1.40)
1 (smallest)	0.70 (0.39-1.35)	0.91 (0.46-1.79)
Retinal venular diameters		
1 (smallest)	1.00 (Reference)	1.00 (Reference)
2	2.17 (1.04-4.52)	1.81 (0.85-3.85)
3	2.23 (1.07-4.66)	1.98 (0.93-4.20)
4 (largest)	1.98 (0.93-4.22)	1.48 (0.66-3.31)
Arteriolar-to-venular ratio		
4 (largest)	1.00 (Reference)	1.00 (Reference)
3	1.47 (0.78-2.76)	1.66 (0.84-3.28)
2	1.24 (0.64-2.39)	1.45 (0.71-2.95)
1 (smallest)	0.78 (0.38-1.63)	0.92 (0.41-2.07)

* OR with corresponding 95% confidence interval, n=3469.

† Adjusted for age, gender, and follow-up time.

‡ Adjusted for age, gender, follow-up time, diabetes mellitus, smoking, total-to-HDL cholesterol ratio, mean perfusion pressure, and intima-media thickness.

Table 4.4 Mean Change of Optic Disc Dimensions in Quartiles of Baseline Retinal Vessel Diameters*

	Cup Area (mm^2)	Rim Area (mm^2)	VCDR†
Retinal arteriolar diameters			
4 (largest)	0.030 (0.018; 0.042)	0.024 (0.008; 0.039)	0.005 (0.000; 0.010)
3	0.014 (0.002; 0.026)	0.028 (0.013; 0.043)	0.003 (-0.002; 0.008)
2	0.019 (0.007; 0.031)	0.027 (0.012; 0.043)	0.005 (0.000; 0.009)
1 (smallest)	0.021 (0.009; 0.033)	0.037 (0.022; 0.052)	0.005 (0.001; 0.010)
Test for trend	$P = 0.33$	$P = 0.67$	$P = 0.97$
Retinal venular diameters			
1 (smallest)	0.024 (0.012; 0.036)	0.032 (0.016; 0.047)	0.005 (0.000; 0.010)
2	0.016 (0.003; 0.027)	0.034 (0.019; 0.050)	0.003 (-0.002; 0.008)
3	0.013 (0.001; 0.024)	0.034 (0.019; 0.050)	0.001 (-0.004; 0.006)
4 (largest)	0.033 (0.021; 0.045)	0.016 (0.000; 0.031)	0.008 (0.003; 0.013)
Test for trend	$P = 0.08$	$P = 0.28$	$P = 0.25$
Arteriolar-to-venular ratio			
4 (largest)	0.024 (0.012; 0.036)	0.026 (0.011; 0.042)	0.004 (-0.001; 0.009)
3	0.013 (0.001; 0.025)	0.036 (0.020; 0.051)	0.002 (-0.003; 0.007)
2	0.018 (0.007; 0.030)	0.031 (0.016; 0.046)	0.004 (-0.001; 0.009)
1 (smallest)	0.029 (0.017; 0.041)	0.023 (0.008; 0.039)	0.008 (0.003; 0.013)
Test for trend	$P = 0.29$	$P = 0.70$	$P = 0.50$

* Age and gender adjusted mean changes with corresponding 95% confidence interval, n=2782.

† VCDR, vertical cup-to-disc ratio.

Discussion

In this prospective study in community-dwelling elderly people, our main finding was that both retinal arteriolar and venular diameters at baseline were not related to an increased risk of OAG. In line with these observations, the retinal vessel diameters did not predict incident optic disc changes.

A potential limitation of our study is the reduced number of participants at follow-up, owing to the large number of deaths that occurred during follow-up in this elderly cohort. If persons who died before the follow-up examination had OAG

before death more often than those who survived, this would have biased the results towards the null value. However, we have previously shown that people who have OAG are not at an increased risk of death, excluding the possibility that survival bias explains our negative findings.[32] Furthermore, persons who died before the follow-up examination and those who refused to participate showed statistically significant differences from the participants in cardiovascular profile, but the retinal vessel diameters were not different, suggesting a limited role for selective nonresponse. This loss to follow-up probably resulted in the imprecision of an underlying association, leading to larger confidence intervals. Hence, we cannot rule out the possibility that we were unable to detect small effects due to the small number of incident cases. Another limitation was that photographs were not taken synchronized on the cardiac cycle, leading to variation in vessel diameter due to pulsatility.[33] However, because photography was independent of any characteristic of the participants, this would have caused random misclassification.

Strengths of the present study are its prospective population-based design, a large number of community-dwelling elderly persons, accurate and objective quantification of retinal vessel diameters, and standardized definitions for iOAG.

In systemic hypertension, the increased peripheral vascular resistance may impair ocular perfusion.[34] In the Rotterdam Study, blood pressure was associated with prevalent high-tension OAG (OR per standard deviation increase in pulse pressure, 1.32; 95% CI, 1.03-1.69), but not with prevalent normal-tension OAG (OR, 0.97; 95% CI, 0.82-1.15) (Hulsman et al., personal communication, November 2004). The increased risk of high-tension OAG was partly due to the positive correlation between blood pressure and IOP.[7, 11] However, it remains unclear whether high blood pressure, independent of its effect on IOP, is related to OAG.[34] No such relationship was established in either the Barbados Eye Study (OR, 1.29; 95% CI, 0.65-2.59),[11] or the Baltimore Eye Survey (OR, 1.32; 95% CI, 0.60-2.92).[7] Alternatively, hypotension rather than hypertension has been proposed to be deleterious to the optic nerve function.[9, 34] A decreased diastolic perfusion pressure was related to prevalent OAG (OR, 3.29; 95% CI, 2.06-5.28).[11] It remains to be determined, however, to what extent systemic blood pressure is representative of the local perfusion of the optic nerve head and the retinal ganglion cell layer.[11]

Few studies thus far have examined the relationship between retinal vessel abnormalities and OAG. One study showed that patients with OAG had significantly smaller arteriolar diameters (n=281; mean, 91 ± 20 μm), measured on optic disc photographs, than age-matched control persons (n=173; mean, 104 ± 18 μm).[12] In a

population-based cross-sectional study, prevalent OAG cases (n=59; mean, 183 µm) also had smaller arteriolar diameters compared with control cases (n=3065; mean, 194 µm).[35] Conversely, in another study involving digital scanning laser fluorescein angiography, no differences in either arteriolar or venular diameters were observed in patients with OAG compared with control persons, although retinal arteriovenous circulation time was substantially prolonged.[36] Clinically, it is also known that reduced retinal blood perfusion, such as in central retinal artery occlusion or nonarteritic anterior ischemic optic neuropathy, often does not lead to glaucomatous cupping.[14, 37] Our prospective data provide evidence against a retinal vascular cause in the pathogenesis of retinal ganglion cell loss and the subsequent development of GVFL. Only in the categorized analysis did it seem that larger venular diameters were related to iOAG. However, there was no clear trend, and this association disappeared after additional adjustments. The results of the linear models for iOAG (Table 4.2) and the models for optic disc changes (Table 4.4) also support the view that this association is a spurious finding.

For proper interpretation of these results, local differences in ocular circulation should be discussed.[9, 38] The inner part of the retina (including the retinal ganglion cell layer) and the surface layer of the optic nerve head are vascularized by the retinal arterioles, whereas the main sources of blood supply to the optic nerve head are the short posterior ciliary arteries, either directly or from the circle of Haller and Zinn.[38] It has been reported that the autoregulation in the short posterior ciliary arteries seems to be less efficient than in the retinal circulation.[9] Also, in contrast to the retinal vessels, the optic nerve head vasculature has no proper blood-tissue barrier, making it more sensitive to fluctuating levels of vasoactive molecules (such as angiotensin-II).[9] Because of these differences, the short posterior ciliary arteries may be more vulnerable to vascular damage than the retinal vessels. This notion is supported by several studies suggesting that, in OAG, impairment in blood flow is more prominent in the short posterior ciliary arteries than in the retinal arteries.[13, 15, 39]

Animal models have also suggested that the retinal circulation may not be causally related to OAG.[40] Administration of endothelin-1, a vasoconstrictive agent that reduces, among others, the retinal blood flow, resulted in loss of retinal ganglion cells and their axons in rats,[40] probably mediated by apoptosis.[41] However, this type of vascular injury did not lead to optic disc cupping.[40] It has been suggested that remodeling of the extracellular matrix, irrespective of the origin of retinal ganglion cell loss, is the hallmark of optic disc cupping.[40] Activation of quiescent astrocytes

(for example by an increase in IOP) could lead to an increased expression of metalloproteinases, enzymes that play an important role in remodeling the optic disc and eventually leading to cupping.[42]

In conclusion, we have shown that baseline retinal vessel diameters did not increase the risk of iOAG or incident glaucomatous optic disc changes. The results reported herein provide no evidence for a retinal vascular role in the pathogenesis of OAG. Further prospective studies should be conducted to confirm these findings and to elucidate the possible role of vascular factors in the pathophysiology of OAG.

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5

Diabetes Mellitus and Risk of Open-Angle Glaucoma

Abstract

Purpose

To investigate the association between diabetes mellitus and incident open-angle glaucoma (iOAG).

Design

Prospective population-based cohort study.

Participants

Participants aged 55 years and older from the Rotterdam Study, The Netherlands, who were at risk of iOAG.

Methods

Participants at risk of iOAG underwent at baseline (1990-1993) and follow-up (1997-1999) the same ophthalmic examination including intraocular pressure measurement, visual field testing and simultaneous stereo optic disc photography. At baseline, diabetes mellitus was defined as the use of anti-diabetic medication, and/or a random or post-load glucose value ≥ 11.1 mmol/l. The diagnosis of OAG was based on an algorithm using optic disc measures and visual field test results, independent of the intraocular pressure.

Main Outcome Measure

Incident OAG.

Results

In total 3837 participants without OAG at baseline were reexamined. After a mean follow-up time of 6.5 years, iOAG developed in 87 persons. The relative risk of iOAG associated with baseline diabetes was 0.82 (95% confidence interval, 0.33-2.05). After adjustment for age, gender, follow-up time, intraocular pressure, intraocular pressure-lowering treatment, body mass index, and systemic hypertension, the relative risk of iOAG was 0.65 (95% confidence interval, 0.25-1.64).

Conclusions

In this prospective, population-based study, diabetes mellitus was not a risk factor of iOAG.

Introduction

Open-angle glaucoma (OAG) may be characterized by glaucomatous optic neuropathy (GON) and glaucomatous visual field loss (GVFL), after exclusion of angle-closure and secondary glaucoma. It is a progressive disease, eventually leading to blindness that has substantial impact on daily life functioning of people. Due to aging populations, the burden of OAG on societies will increase.[1] Among risk factors, such as elevated intraocular pressure (IOP), age, race, myopia, positive family history, and pseudoexfoliation syndrome, only IOP can be effectively modulated.[2] Another possible risk factor that can be influenced is diabetes mellitus. Some studies have found an association between diabetes and prevalent OAG in a general population,[3-5] while others did not.[6-10] Two longitudinal studies on the relation between prevalent diabetes and incident OAG (iOAG) have been performed. One study in Scotland measuring the association from prescription and morbidity record databases did not show a significant difference in incidence of OAG between persons with and without diabetes,[11] nor did a large population-based study from Melbourne.[12]

We prospectively studied associations between baseline diabetes mellitus and iOAG in the general elderly population.

Methods

Study population

The ophthalmic part of the Rotterdam Study, a prospective, population-based cohort study of residents aged 55 years and older, living in a district of Rotterdam has been described previously (response 78%).[13, 14] In brief, home interviews and ophthalmic examinations at the examination center were conducted after the appropriate medical ethics committees had approved the study protocol and all participants had given a written informed consent, according to the Declaration of Helsinki. After the baseline examination in 1990-1993, the first follow-up examination focusing on iOAG was performed in 1997-1999.

Assessment of diabetes mellitus and covariates

During the home interviews current medicine use was assessed. Nonfasting serum blood samples were collected at baseline. Participants without known diabetes underwent also a nonfasting glucose tolerance test (85% of the total population).[15]

Diabetes mellitus at baseline was defined as the use of anti-diabetic medication, and/or a random or post-load glucose value ≥ 11.1 mmol/l.[16]

Body mass index was calculated from height and weight (weight/height^2 (kg/m^2)). We defined systemic hypertension as systolic blood pressure ≥ 160 mmHg, or diastolic blood pressure ≥ 100 mmHg, or use of blood pressure lowering medication, with hypertension as indication, or a combination of these.

Assessment of open-angle glaucoma

The ophthalmic examination included Goldmann applanation tonometry,[17] visual field screening, followed by ophthalmoscopy and stereoscopic fundus photography in pharmacological mydriasis. The procedures were the same at baseline and at follow-up.[18, 19]

The diagnosis of OAG was based on an algorithm using GON and GVFL, and could only be made in persons who had at least in one and the same eye an open anterior chamber angle and no history or sign of angle closure or secondary glaucoma. For GON evaluation, simultaneous stereo color transparencies were digitized and analyzed with a semi-automated image analyzer.[13, 19] If the transparencies were absent or of bad quality, ophthalmoscopic estimates were used. Possible GON was defined as vertical cup-to-disc ratio ≥ 0.7, or asymmetry between eyes of ≥ 0.2, or minimum rim width < 0.1 and probable GON as vertical cup-to-disc ratio ≥ 0.8, or asymmetry between eyes of ≥ 0.3, or minimum rim width < 0.05.[13] The visual fields were screened with automated suprathreshold perimetry and defects were confirmed by Goldmann perimetry. Visual field loss, compatible with OAG (thus excluding hemianopia, quadrantanopia or isolated central defect) and not explained by other (neuro-) ophthalmic causes was defined as GVFL.[18] Definite OAG was defined as the presence of possible or probable GON *and* GVFL; probable OAG as probable GON *without* GVFL or presence of GVFL *without* any GON. Possible OAG referred to possible GON only.[13] Incident OAG was defined as no or possible OAG in either eye at baseline and probable or definite OAG in at least one eye at follow-up.[19] Excluded from this incidence definition were persons with possible GON at baseline and probable GON at follow-up as the only change because a tiny increase in one of the GON criteria could lead to a change in this classification. Also because we wanted to be as confident as possible that we really analyzed cases with iOAG for risk analyses.

Population for analysis and data analysis

At baseline, 6780 participants underwent an ophthalmologic examination. After excluding persons with prevalent definite or probable OAG (n=221) and persons without information on diabetes at baseline (n=27), 6532 participants formed the cohort at risk for developing iOAG.

We used univariate analyses of covariance to compare baseline characteristics of participants and nonparticipants in the follow-up examination, adjusted for age and gender when appropriate. Logistic regression analyses were used to calculate odds ratios, which can be interpreted as relative risks. In further analyses we adjusted for age, gender, follow-up time, IOP, IOP-lowering treatment, body mass index and systemic hypertension, with corresponding 95% confidence intervals (CIs). All analyses were performed with SPSS for Windows, version 11 (SPSS Inc., 2001, Chicago, IL).

Results

After a mean follow-up time of 6.5 years (range, 5.0-9.4), 3837 persons at risk for iOAG participated in the follow-up examination. Of the nonparticipants, 46% (n=1233) died and 54% (n=1462) refused or were unable to attend the follow-up examination. Table 5.1 presents baseline characteristics of the study population. The nonparticipants were on average older, more often female and more often had diabetes or systemic hypertension. Table 5.2 shows that baseline OAG characteristics for persons with diabetes were not statistically significant between participants and those who refused to participate.

Incident OAG developed in 82 out of 3573 persons without and in 5 out of 264 persons with diabetes. Persons with diabetes at baseline had a relative risk of iOAG of 0.82 (95% CI, 0.33-2.05) compared to persons without diabetes (Table 5.3). After adjustment for confounders this relative risk was 0.65 (95% CI, 0.25-1.64). We found no differences in relative risks between participants aged 55 to 75 years and persons aged 75 years and older.

Among the participants at follow-up, 3.0% of those with diabetes mellitus received IOP-lowering treatment at baseline compared to 1.7% of those without diabetes mellitus. After adjusting for age and gender, this difference was not significant (relative risk, 1.60; 95% CI, 0.76-3.41).

Table 5.1 Baseline Characteristics of 6532 Persons at Risk for Incident Open-Angle Glaucoma

	Status at Follow-Up				
	Participated (n = 3837)	Declined or Unable (n = 1462)	*P* Value	Died (n = 1233)	*P* Value
Age, y ± SD	65.7 ± 6.9	71.2 ± 8.7	<0.001	77.3 ± 9.1	<0.001
Female, %	60.3	67.1	<0.001	48.4	<0.001
Diabetes mellitus, %	7.9	10.0	0.03	18.6	<0.001
Vertical cup-to-disc ratio*	0.52	0.50	<0.001	0.49	<0.001
Possible OAG, %	8.1	7.1	0.08	7.0	0.11
IOP ± SD, mmHg†	15.0 ± 3.1	15.2 ± 3.4	0.15	14.8 ± 3.4	0.10
IOP-lowering treatment, %	2.1	2.6	0.31	1.4	0.18
Systemic hypertension, %	31.1	36.6	<0.001	40.8	<0.001
Body mass index ± SD, kg/m^2	26.3 ± 3.5	26.6 ± 3.9	0.06	25.8 ± 3.9	<0.001

All values are adjusted for age and gender, when appropriate. *P* values are based on comparisons with participants. SD = standard deviation; OAG = open-angle glaucoma.

* Measured as maximum vertical cup-to-disc ratio of both eyes.

† Intraocular pressure in eye with highest IOP; persons with IOP-lowering treatment were excluded.

Table 5.2 Baseline Ophthalmic Characteristics of 677 Persons with Diabetes Mellitus at Baseline

	Status at Follow-Up				
	Participated (n = 264)	Declined or Unable (n = 155)	*P* Value	Died (n = 258)	*P* Value
Vertical cup-to-disc ratio*	0.51	0.49	0.26	0.48	0.18
IOP, mmHg†	16.0	15.7	0.43	15.2	0.02
IOP-lowering treatment, %	3.6	3.2	0.83	2.6	0.56
Possible OAG, %	9.9	9.3	0.74	6.9	0.12

All values are adjusted for age and gender, when appropriate. *P* values are based on comparisons with participants. OAG = open-angle glaucoma.

* Measured as maximum vertical cup-to-disc ratio of both eyes.

† Intraocular pressure in eye with highest IOP; persons with IOP-lowering treatment were excluded.

Table 5.3 Relative Risks of Incident Open-angle Glaucoma in Persons with and without Prevalent Diabetes Mellitus

				Relative Risk (95% Confidence Interval)		
		No. at Risk	Cases	Model 1*	Model 2†	Model 3‡
Diabetes	No	3573	82	0.82	0.72	0.65
Mellitus	Yes	264	5	(0.33-2.05)	(0.29-1.80)	(0.25-1.64)

* Unadjusted.

† Adjusted for age, gender and follow-up time.

‡ Adjusted for age, gender, follow-up time, intraocular pressure, intraocular pressure-lowering treatment, body mass index and systemic hypertension.

Discussion

In our study we could not detect an association between diabetes mellitus and iOAG. This was in line with two other prospective studies,[11, 12] but in contrast with a recent meta-analysis, performed on five case-control studies and seven cross-sectional studies, concluding that diabetes was a risk factor of OAG.[20] This could be due to different definitions of diabetes and OAG or to the fact that in the meta-analysis two studies that did not find a relationship were excluded.[7, 8] For a diabetes diagnosis, medication use, fasting, nonfasting or post-load blood glucose levels, or self-reported diabetes are customary, while the definitions of OAG varied widely over these studies.[3, 5, 6, 11, 12]

Halfway baseline we presented a relative risk of 3.11 (95% CI, 1.12-8.66) for the risk of persons with diabetes to have prevalent OAG.[4] We changed however, between the first and final analysis of the baseline cohort,[4, 13] our OAG definition. When we recalculated the relative risk at baseline on the whole cohort with the present definitions in this longitudinal analysis, the risk dropped to a nonsignificant 1.40 (95% CI, 0.96-2.03), adjusted for age, gender and body mass index.[13]

Selection bias, in the form of selective nonresponse, could distort the results. The nonparticipants indeed had significantly more often diabetes than the participants at baseline, and this could affect the extrapolation of our findings to the general population. However, nonresponse to the follow-up examination appeared to be only related to their diabetes and not to their risk of iOAG, as is shown in Table 5.2 with the ocular risk factors.

The number of deaths that occurred during follow-up in this elderly cohort could also lead to selection bias. If persons who died between baseline and follow-up developed OAG more often than those who survived, this would have biased the results toward the null value. However, there are two studies showing that people who have OAG are not at an increased risk of death, making survival bias as an explanation for our negative findings less likely.[21, 22]

Another potential problem could have been that in The Netherlands, patients with diabetes more often visit their ophthalmologist to check for retinopathy than persons without diabetes and might therefore be more often diagnosed with ocular hypertension or beginning OAG. This could have led to fewer iOAG cases, had they received more IOP-lowering treatment.[23] The difference in participants with IOP-lowering treatment at baseline appeared not to be significant in our study. Therefore, we do not think that this explains our results.

Participants and nonparticipants differed in age and gender. This could have led to an underestimation of the number of iOAG cases. At the time of follow-up, the older nonparticipants were more often institutionalized and consequently not able to undergo complete ophthalmologic examination due to mental and physical disabilities, while OAG occurs more often in the higher age groups.

Strengths of this study are the population-based and prospective design, relatively large size of the cohort, collection of perimetry and other data necessary for the OAG diagnosis in all participants, and the clear diagnostic criteria for diabetes and OAG. In case data are taken from existing patient files, thus not screening all participants for OAG, selection bias could have occurred.[11] The sample size of our study was quite large. However, due to the low incidence of OAG, not many iOAG cases were found and we still lacked power to demonstrate small differences. That is why we combined probable and definite OAG in iOAG. When we based our analyses only on the 29 definite iOAG cases, the relative risk of iOAG in diabetic persons was 1.04 (95% CI, 0.30-3.66; fully adjusted model).

The wide CIs of our estimates hamper interpretation of the results. As mentioned, we opted for strict OAG criteria leaving borderline cases rather out than in. In our data we could not find an association between diabetes mellitus and iOAG in line with other cohort studies.[11, 12] We cannot exclude the possibility that there is a small effect of diabetes on the risk of iOAG. The rather low incidence of OAG stresses the necessity to make OAG definitions and diagnoses worldwide more comparable, so that in the future studies can reliably be pooled for a meta-analysis to improve these estimates.

In conclusion, this study does not confirm that diabetes mellitus is a risk factor of iOAG.

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6

Atherosclerosis, C-reactive Protein, and Risk of Open-Angle Glaucoma

Abstract

Purpose

To test the hypothesis that atherosclerosis and serum C-reactive protein (CRP) levels are risk factors for open-angle glaucoma (OAG).

Methods

In a prospective population-based cohort study, all participants aged 55 years and over and at risk of incident OAG, underwent at baseline (1990-1993) and follow-up (1997-1999) the same ophthalmic examination including visual field testing and stereo optic disc photography. At baseline, atherosclerosis was assessed by means of echography of the carotid arteries, abdominal x-ray examination, ankle-arm index, and serum CRP levels were determined. The diagnosis of OAG was based on an algorithm using optic disc measures and visual field loss. Odds ratios of OAG were computed with logistic regression analyses. Risk factors were categorized in tertiles.

Results

After a mean follow-up of 6.5 years, incident OAG was diagnosed in 87 (2.3%) out of 3842 participants at risk of OAG. Carotid artery plaques and intima-media thickness, aortic calcifications, ankle-arm index nor levels of CRP were risk factors for OAG. Odds ratios, given for the highest versus lowest tertile, were for carotid plaques 1.43 (95% confidence interval (CI), 0.68-2.99), for carotid intima-media thickness 0.86 (95% CI, 0.47-1.57), for aortic calcifications 1.02 (95% CI, 0.60-1.75), for the ankle-arm index 0.69 (95% CI, 0.38-1.25), and for CRP 1.19 (95% CI, 0.68-2.07).

Conclusions

In this prospective, population-based study, neither atherosclerosis nor serum CRP levels were related to incident OAG.

Introduction

Open-angle glaucoma (OAG) may be characterized as a disease of the optic nerve with cupping of the optic disc and loss of nerve fibers, so-called glaucomatous optic neuropathy (GON). In a later stage, glaucomatous visual field loss (GVFL) can occur. It is a progressive disease, eventually leading to blindness that has substantial impact on daily functioning of people. Due to aging populations, the burden of OAG on societies will increase.[1] The etiology of this process has still to be elucidated. One out of many theories is impaired perfusion of the optic disc, possibly caused by autonomous vessel dysfunction or atherosclerosis.

Atherosclerosis is a systemic disease affecting arteries of all sizes, including the small ocular ones.[2, 3] Through thickening of the intima and development of plaques the vessel lumen decreases, eventually leading to disturbed perfusion and ischemia.[4]

Non-invasive ways to measure atherosclerosis include echography of the carotid arteries for determination of the intima-media thickness and presence of plaques, abdominal x-rays for quantifying the amount of calcification in the aorta, and the ankle-arm index.

Inflammation appears to play a role in the process of atherosclerosis. Serum C-reactive protein (CRP), a general marker of inflammation, has been associated with the occurrence of atherosclerosis,[5, 6] and the level of CRP gives an indication for the severity of atherosclerosis.[7] The question if CRP is only a proxy or causally related to atherosclerosis has not been fully elucidated yet.[5, 6, 8] Information on the role of inflammatory factors as a cause for primary OAG is hardly available. To our knowledge, no population-based studies have looked into atherosclerosis or serum CRP as risk factors for OAG and that is why we investigated if atherosclerosis or peripheral inflammation were risk factors for OAG in a general elderly population.

Methods

Study population

The ophthalmic part of the Rotterdam Study, a prospective, population-based cohort study of residents aged 55 years and older, living in a district of Rotterdam has been described previously.[9, 10] In short, home interviews and examinations at the examination center were conducted after the appropriate medical ethics committees

had approved the study protocol and all participants had given a written informed consent, according to the Declaration of Helsinki. After the baseline examination, from 1990 through 1993, a follow-up examination to study incident OAG was performed from 1997 through 1999.[11]

Measures of atherosclerosis and CRP

Carotid atherosclerosis was determined through ultrasonography of both carotid arteries with a 7.5-MHz linear-array transducer and a duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington). The intima-media thickness was measured in the common carotid arteries and the presence of plaques was determined in both common and internal carotid arteries and bifurcations.[12] We computed a weighted plaque score ranging from 0 to 6 by adding the number of sites at which a plaque was detected, divided by the total number of sites for which an ultrasonographic image was available, multiplied by 6 (the maximum number of sites).[13] The maximum common carotid intima-media thickness was measured over a length of 10 mm, with as reference point the beginning of the dilatation of the distal common carotid artery and the average of near- and far-wall measurements, and of left and right common carotid arteries was computed.[12]

We diagnosed abdominal atherosclerosis by radiographic detection of calcified deposits in the aorta on a lateral abdominal film.[14] The extent of aortic calcification was classified, according to the length of the involved area (0, ≤ 1.0 cm, 1.1 to 2.4 cm, 2.5 to 4.9 cm, 5.0 to 9.9 and ≥ 10 cm, respectively). This resulted in scores from 0 to 5.[15]

Lower-extremity atherosclerosis was expressed as the ankle-arm index. Systolic blood pressure at the ankles (posterior tibial artery) was measured in supine position with a random-zero sphygmomanometer and an 8-MHz continuous-wave Doppler probe (Huntleigh 500D, Huntleigh Technology, Bedfordshire, UK). The ratio of the systolic blood pressure at the ankle and the systolic blood pressure at the arm was the ankle-arm index. The lowest index of both sides was used in the analyses.[16] Because arterial rigidity prevents arterial compression and therefore will lead to spuriously high values of the ankle-arm index, an index > 1.50 was considered invalid.[17]

Nonfasting blood was collected at baseline, and all tubes were stored on ice before and after blood sampling. High-sensitivity CRP was determined in serum, which was stored at -20°C until performance of the CRP measurements in 2003-2004. We measured CRP using Rate Near Infrared Particle Immunoassay (Immage®

Immunochemistry System, Beckman Coulter, Fullerton, CA). Outliers (values > 3 standard deviations of the population distribution) of logarithmically transformed CRP were excluded since they might indicate the presence of an active inflammatory disease.

Assessment of open-angle glaucoma

The procedure for the assessment of OAG has been described before.[9, 10] In short, the ophthalmic examination included Goldmann applanation tonometry,[18] visual field screening, followed by ophthalmoscopy and stereoscopic fundus photography in pharmacological mydriasis with similar procedures at baseline and follow-up.[11, 19]

For GON evaluation, simultaneous stereo color transparencies were digitized and analyzed with a semi-automated image analyzer. If the transparencies were absent or of bad quality, ophthalmoscopic estimates were used. Possible GON was defined as vertical cup-to-disc ratio ≥ 0.7, or asymmetry between eyes of ≥ 0.2 or minimum rim width < 0.1 and probable GON as vertical cup-to-disc ratio ≥ 0.8, or asymmetry between eyes of ≥ 0.3 or minimum rim width < 0.05.[9] The visual fields were screened with automated suprathreshold perimetry and a defect in any eye, defined as nonresponse to a light stimulus in at least three contiguous tests points or in four contiguous test points when the blind spot was included, was checked by Goldmann perimetry on both eyes.[19] Visual field loss, compatible with OAG (thus excluding hemianopia, quadrantanopia or isolated central defect) and not explained by other (neuro-) ophthalmic causes was defined as GVFL.[10, 19]

The diagnosis OAG was based on an algorithm using GON and GVFL, independent of the intraocular pressure, and could only be made in participants who had at least in one and the same eye an open anterior chamber angle and no history or signs of angle closure or secondary glaucoma.[9, 11] Definite OAG was defined as the presence of possible or probable GON *and* GVFL; probable OAG as probable GON *without* GVFL or presence of GVFL *without* any GON. Possible OAG referred to possible GON only.[9] Incident OAG was defined as no or possible OAG in either eye at baseline and probable or definite OAG in at least one eye at follow-up.[11] Excluded from this incidence definition were persons with possible GON at baseline and probable GON at follow-up as the only change because a tiny increase in one of the GON criteria could lead to a change in this classification. This mainly because we wanted to be as confident as possible that we really used cases with incident OAG in the risk analyses. We prefer to speak of OAG instead of primary OAG because at

baseline we did not specifically exclude pseudoexfoliation glaucoma. This, however, was never encountered at follow-up.

Population for analysis and data analysis

At baseline, 6780 participants (78% of eligibles) underwent an ophthalmologic examination. After excluding persons with prevalent definite or probable OAG (n=221), and those without data on both perimetry and optic disc measures (n=7), 6552 participants formed the cohort at risk for incident OAG.

Data on carotid plaques were available in 5385 persons, carotid intima-media thickness in 5417, aortic atherosclerosis in 5520, peripheral atherosclerosis in 5890, and serum CRP levels in 6111 persons. Due to an ankle-arm index > 1.50 we excluded 34, and to CRP outliers 27 participants.

We used univariate analyses of covariance to compare baseline characteristics of participants and nonparticipants in the follow-up examination, when appropriate adjusted for age and gender. Serum CRP was log-transformed in the analyses with standard deviations because its distribution was skewed. Logistic regression analyses were used to calculate odds ratios with corresponding 95% confidence intervals, which can be interpreted as relative risks. In further analyses we adjusted for age, gender and follow-up time. The carotid intima-media thickness, ankle-arm index, and CRP were analyzed in tertiles and per standard deviation. The determinants carotid plaques and aortic calcification were categorized in three groups and analyzed according to these groups or per category increase. All analyses were performed with SPSS for Windows, version 11 (SPSS Inc., 2001, Chicago, IL).

Results

After a mean follow-up time of 6.5 years (range, 5.0-9.4), 1244 (19%) participants had died and 1466 (22%) declined or were unable to participate in the follow-up examination, leaving 3842 persons.

Baseline characteristics of the population-at-risk are provided in Table 6.1. Most variables were significantly different between participants and those who refused or died. This did not hold for the OAG-related variables.

Incident OAG was diagnosed in 87 persons. Table 6.2 shows that baseline atherosclerosis, analyzed in tertiles, groups, and per standard deviation or category, was not associated with incident OAG. There seemed to be a trend with the increase

Table 6.1 Baseline Characteristics of 6552 Persons at Risk for Incident Open-Angle Glaucoma

	Status at Follow-Up		
	Participated (n = 3842)	Declined or Unable (n = 1466)	Died (n = 1244)
Age, y	65.7 ± 6.9	71.2 ± 8.7 ¶	77.4 ± 9.1 ¶
Female gender, %	57.8	68.6 ¶	54.3 ¶
Vertical cup-to-disc ratio*	0.53 ± 0.13	0.50 ± 0.15 ¶	0.48 ± 0.17 ¶
Possible open-angle glaucoma, %	7.9	7.2	7.6
Intraocular pressure, mmHg†	15.1 ± 3.1	15.2 ± 3.4	14.8 ± 3.4
Intraocular pressure lowering treatment, %	1.8	2.7	2.3
Body mass index, kg/m^2	26.3 ± 3.5	26.7 ± 4.0 ¶	25.8 ± 3.9 ¶
Diabetes mellitus, %	6.9	10.6 ¶	20.9 ¶
Systemic hypertension, %	28.9	38.4 ¶	45.5 ¶
Total cholesterol, mmol/l	6.7 ± 1.2	6.7 ± 1.2	6.3 ± 1.3 ¶
HDL cholesterol, mmol/l	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4 ¶
History of stroke, %	1.3	3.5 ¶	7.2 ¶
Demented, %	0.2	3.4	15.2 ¶
Intima-media thickness, mm	0.77 ± 0.14	0.81 ± 0.16 ¶	0.89 ± 0.18 ¶
Carotid plaques score‡	1.28 ± 1.56	1.68 ± 1.72 ¶	2.40 ± 1.90 ¶
Aortic calcification score§	1.47 ± 1.39	1.93 ± 1.48 ¶	2.32 ± 1.48 ¶
Ankle-arm index	1.11 ± 0.18	1.03 ± 0.23 ¶	0.91 ± 0.29 ¶
C-reactive protein, mg/l#	1.57 ± 2.65	1.90 ± 2.62 ¶	2.74 ± 3.03 ¶

Data are unadjusted means ± standard deviation for continuous variables and percentages for dichotomous variables.

* Measured as maximum vertical cup-to-disc ratio of both eyes.

† Measured as maximum intraocular pressure in any of both eyes; persons with intraocular pressure lowering treatment were excluded.

‡ Score ranges from 0 through 6.

§ Score ranges from 0 through 5.

\# Based on mean from the natural logarithm (back-transformed).

¶ Significant ($P < 0.05$) compared with participants, adjusted for age and gender if applicable.

Table 6.2 Relative Risks of Incident Open-Angle Glaucoma According to Amount of Baseline Atherosclerosis

Atherosclerosis	No. at Risk	Cases	Relative Risk (95% Confidence Interval) Model 1*	Model 2†
Carotid plaques				
Low	1525	25	1.00	1.00
Intermediate	1315	38	1.79 (1.07-2.97)	1.55 (0.92-2.61)
High	389	11	1.75 (0.85-3.58)	1.43 (0.68-2.99)
Per category increase	3229	74	1.40 (1.02-1.93)	1.26 (0.90-1.75)
Carotid intima-media thickness				
Low	1080	23	1.00	1.00
Intermediate	1085	24	1.04 (0.58-1.85)	0.84 (0.47-1.53)
High	1082	29	1.27 (0.73-2.20)	0.86 (0.47-1.57)
Per SD increase	3247	76	1.11 (0.89-1.38)	0.95 (0.75-1.22)
Aortic calcification				
Low	1358	32	1.00	1.00
Intermediate	1263	23	0.77 (0.45-1.32)	0.63 (0.36-1.09)
High	874	29	1.42 (0.85-2.37)	1.02 (0.60-1.75)
Per category increase	3495	84	1.18 (0.90-1.55)	1.01 (0.75-1.34)
Ankle-arm index				
Low	1172	21	0.77 (0.43-1.37)	0.69 (0.38-1.25)
Intermediate	1171	27	1.00 (0.58-1.72)	0.98 (0.57-1.70)
High	1174	27	1.00	1.00
Per SD decrease	3517	75	0.90 (0.71-1.15)	0.86 (0.67-1.09)

Ranges (low, intermediate, high): carotid plaques score: 0, 1-3, 4-6; carotid intima-media thickness: 0.41-0.70, 0.70-0.81, 0.81-1.71; aortic calcification score: 0, 1-2, 3-5; ankle-arm index: 0-1.06, 1.06-1.19, 1.19-1.50. SD = standard deviation.

* Unadjusted.

† Adjusted for age, gender and follow-up time.

Table 6.3 Relative Risks of Incident Open-Angle Glaucoma According to Baseline C-Reactive Protein, in Tertiles and per Standard Deviation

			Relative Risk (95% Confidence Interval)	
C-Reactive Protein	No. at Risk	Cases	Model 1*	Model 2†
Low	1205	23	1.00	1.00
Intermediate	1205	33	1.45 (0.85-2.48)	1.40 (0.81-2.40)
High	1208	29	1.26 (0.73-2.20)	1.19 (0.68-2.07)
Per SD increase	3618	85	1.10 (0.88-1.38)	1.06 (0.85-1.34)

Ranges C-reactive protein (low, intermediate, high): 0.20-1.03, 1.04-2.46, 2.47-41.0. SD = standard deviation.

* Unadjusted.

† Adjusted for age, gender and follow-up time.

of number of carotid plaques, but due to statistical power the 95% confidence intervals were too wide to draw a more definite conclusion. Table 6.3 shows that elevated baseline serum CRP levels, analyzed both in tertiles and per standard deviation, also constituted no risk for incident OAG.

Discussion

In our study we could not find an association between atherosclerosis or serum CRP levels at baseline, and incident OAG. Impaired perfusion of the optic disc by atherosclerosis or inflammation is therefore not likely to be a major cause of OAG.

Earlier studies have measured atherosclerosis through echography or x-ray of the carotid arteries in patients with OAG.[20-27] These studies described the occurrence of calcification in clinic-based case series or within specific patients groups, such as low-tension OAG, high-tension OAG, ocular hypertension or healthy controls. Despite some positive findings, a strong association could not be found.[28-31] Another theory states that vascular dysregulation instead of chronically reduced blood flow by atherosclerosis may lead to local vasospasm and to systemic hypotension, which can lead to low perfusion pressure and insufficient autoregulation of the blood supply of the optic nerve head.[3, 29, 31-34] Similarly, vascular dysregulation of other areas such as the brain and the cardiovascular system have been described in glaucoma patients.[35, 36]

The role of inflammation as a risk factor for primary OAG is not as clear as for secondary glaucoma. In secondary glaucoma, inflammatory proteins and cells cause mechanical blockage or damage to the trabeculum, leading to increased intraocular pressure.[37] In what way could inflammation cause primary OAG? During inflammation several acute-phase proteins are released, including CRP. In recent years it has become clear that CRP plays a role in the formation of atherosclerotic plaques.[5-8] In case substances like CRP are repeatedly released due to inflammation, this might facilitate atherosclerosis, which in its turn may impair circulation and can lead to hypoperfusion or even nonperfusion of tissues. In this study we could not demonstrate that this pathway works for OAG as it does for cardiovascular diseases.

Also no elevated level of serum CRP was seen in another study on eight OAG patients.[38]

There is one optic nerve disease that may show cupping like OAG and is associated with inflammation. This is arteritic anterior ischemic optic neuropathy induced by giant cell arteritis.[39] In giant cell arteritis, the vessel walls become infiltrated with monocytes and macrophages, leading to intimal thickening. This can result in arterial thrombosis with its ischemic complications, such as permanent thrombotic occlusion of posterior ciliary arteries with ischemia of the optic nerve head. Levels of CRP and other acute phase proteins are increased in giant cell arteritis.[40] Despite the completely different time-frame in which arteritic anterior ischemic optic neuropathy occurs, the similar morphologic characteristics might indicate a vascular, and possibly an inflammatory pathogenesis for OAG.

With our study, we looked into the possible pathway of atherosclerosis and CRP for OAG. In spite of our large cohort, we had only a limited number of incident OAG cases, due to the prospective, population-based design. By using strict and, as much as possible, objective criteria to diagnose incident OAG, we tried to eliminate misclassification. Some patients might now have been missed as an incident OAG case due to these strict definitions, but for risk analysis it is better to transfer a case into the large control group than contaminate the case group with healthy persons. The limited number of cases affects the precision of our estimates. Had we had more OAG cases, we still estimate that any effect of atherosclerosis or CRP on the incidence of OAG would have remained small.

A potential limitation of our study is the relatively large group of persons who were lost-to-follow-up. This can partially be explained by the large number of deaths that occurred during follow-up in this elderly cohort. However, there are two

studies showing that people who have OAG are not at an increased risk of death, making survival bias as an explanation for our negative findings less likely.[41, 42] Furthermore, participants who refused the follow-up examination differed in several aspects, including the atherosclerosis measures and CRP-levels, compared to those who participated at follow-up. However, it is not likely that among persons with high atherosclerosis or CRP levels, those who left the study would have had a higher risk of OAG than those who participated. Therefore, we do not think that this has biased our results. Thus we assume there is limited bias due to selective response. The age difference between participants and nonparticipants will probably have resulted in fewer incident cases, leading to larger confidence intervals in this study, because the incidence of OAG rises with age.

All measures of atherosclerosis in this study reflect the amount of generalized atherosclerosis. They function as a proxy for atherosclerosis in the vessels, which are important for OAG. We assumed there would be no difference between generalized and localized atherosclerosis, but this also needs to be further explored.

In summary, we were unable to detect an association between atherosclerosis or inflammation and incident OAG.

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7

Polymorphisms of Estrogen Receptor Alpha and Beta, and Risk of Open-Angle Glaucoma

Abstract

Objective

Genetic factors are known to play a role in the etiology of open-angle glaucoma (OAG). Since diminished exposure to estrogens was related to OAG, we investigated if polymorphisms in the estrogen receptor (ER)-α and ER-β gene were associated with incident OAG.

Methods

Participants from the population-based Rotterdam Study aged 55 years and older underwent at baseline and at follow-up the same ophthalmic examination including visual field screening and stereo optic disc photography. Haplotypes of each ER gene were determined. A diagnosis of OAG was based on an algorithm using optic disc measures and visual field loss.

Results

We diagnosed in 87 (2.3%) out of 3842 participants incident OAG after a mean follow-up of 6.5 years. We could not detect any association with ER-α haplotypes. Haplotype 1 of ER-β showed a 3.6 (95% confidence interval, 1.4-9.2) times higher risk of incident OAG in men. In women, no association was found between ER-β and incident OAG.

Conclusions

Polymorphisms in ER-α were not related to OAG, but ER-β polymorphisms led to an increased risk of OAG in men.

Introduction

Open-angle glaucoma (OAG) may be defined as a retinal ganglion cell disorder, characterized by cupping of the optic disc due to loss of nerve fibers, so-called glaucomatous optic neuropathy (GON).[1,2] In a later stage, glaucomatous visual field loss (GVFL) usually occurs. Due to aging populations, the burden of OAG on societies will increase.[3] Little is known about the pathogenesis and etiology of OAG.

Several studies have shown that genetic components are involved in the etiology of OAG.[4-6] Seven chromosomal loci for OAG and associations with other genes were identified.[7-11] In this study, we have chosen to study the genes encoding the two estrogen receptors (ER-α and ER-β). This choice was based on the fact that we previously found an increased risk of OAG in women who went through menopause before age 45 years, suggesting that estrogens could be protective for OAG.[12] This protective effect might be caused by several effects including modification of the intraocular pressure,[13, 14] the retrobulbar circulation,[15, 16] or the extracellular matrix of the optic disc.[17, 18] Neuroprotective properties of estrogens have been described as well.[19, 20]

Single-nucleotide polymorphisms (SNPs), i.e., subtle but common changes in the DNA sequence, can lead to modified activity or structure of the ER protein which as a result could have different responsiveness to circulating estrogens. Estrogens exert their effect by binding to two ERs, which belong to the nuclear receptor hormone superfamily.[21] Possibly, a third, membrane-associated, ER is involved.[22] Estrogens diffuse into the cell nucleus and bind to the receptor to form an estrogen-ER complex. This estrogen-ER complex can subsequently bind to an estrogen response element on a gene to activate its transcription. Both nuclear receptors have been located in several tissues of the eye, including the retinal ganglion cell layer.[20, 23, 24]

The ER-α gene is located on chromosome 6q25 and the ER-β gene on 14q22-24. Two well-known SNPs of the ER-α gene are *PvuII* (rs2234693), located in intron 1, 397 basepairs (bps) upstream of exon 2, and *XbaI* (rs9340799), located in intron 1, 351 bps upstream of exon 2. Polymorphisms of the ER-β gene have been studied less extensively; the most interesting seem rs1256031, located in intron 2, 10550 bps upstream from the start of exon 3, and rs4986938, located 38 bps downstream from the 3-prime untranslated region. The choice of these SNPs was based on their allele frequencies, linkage disequilibrium analysis, and previous reports.[25, 26] The specific functions of ER-α and ER-β are still being explored, but distinct, perhaps even opposite, effects have been described.[21, 27] Through formation

of heterodimers, ER-β is thought to be able to inhibit the transcription activation of ER-α.[28] As a result, specific sets of estrogen-dependent genes could be activated in different tissues, depending on presence or absence of one or both receptors.

The aim of this study was to examine if these four ER-α and ER-β SNPs are a risk factor for OAG.

Methods

Study population

The ophthalmic part of the Rotterdam Study, a prospective, population-based cohort study of residents aged 55 years and older, living in a district of Rotterdam was described previously.[29, 30] Home interviews and examinations at the research center were conducted after the medical ethics committee of the Erasmus Medical Center had approved the study protocol and all participants gave a written informed consent, according to the Declaration of Helsinki. After the baseline examination (1990-1993) for prevalent OAG, a follow-up examination to study incident OAG was performed from 1997 through 1999.

Assessment of open-angle glaucoma

The procedure for the assessment of OAG included Goldmann applanation tonometry and visual field screening, followed by ophthalmoscopy and stereoscopic fundus photography in pharmacological mydriasis with similar procedures at baseline and follow-up.[29-33]

For GON evaluation, simultaneous stereo color transparencies were digitized and analyzed with a semi-automated image analyzer. If the transparencies were absent or of bad quality, ophthalmoscopic estimates were used. Possible GON was defined as vertical cup-to-disc ratio ≥ 0.7, or asymmetry between eyes ≥ 0.2, or minimum rim width < 0.1. Probable GON as vertical cup-to-disc ratio ≥ 0.8, or asymmetry between eyes ≥ 0.3 or minimum rim width < 0.05.[29] Visual fields were screened with automated suprathreshold perimetry and defects were checked by Goldmann perimetry.[32] Visual field loss, compatible with OAG (thus excluding hemianopia, quadrantanopia, or isolated central defect) and not explained by other (neuro-) ophthalmic causes was defined as GVFL.[30, 32]

The diagnosis of OAG was based on an algorithm using GON and GVFL, independent of the intraocular pressure, and could only be made in participants who had at least in one and the same eye an open anterior chamber angle and no history or sign of angle closure or secondary glaucoma.[29, 33] Definite OAG was defined as the presence of possible or probable GON *and* GVFL; probable OAG as probable GON *without* GVFL or presence of GVFL *without* any GON.[29] Incident OAG was defined as no OAG in any eye at baseline and probable or definite OAG in at least one eye at follow-up.[33] Excluded from this incidence definition were persons with as the only change possible GON at baseline and probable GON at follow-up, because a tiny increase in one of the GON criteria could lead to a change in this classification. This mainly because we wanted to be as confident as possible for the risk analyses that we really analyzed cases with incident OAG. We prefer to speak of OAG instead of primary OAG because, at baseline, we did not specifically exclude pseudoexfoliation OAG. This, however, was never encountered at follow-up.

Genotyping

Genotypes of the ER-α and ER-β SNPs were determined using the Taqman allelic discrimination assay. Primer and probe sequences were optimized using the SNP assay-by-design service of Applied Biosystems (Nieuwerkerk aan den IJssel, The Netherlands). For details see http://store.appliedbiosystems.com. Reactions were performed on the Taqman Prism 7900HT 384 wells format.[25] We used the genotype data for each of the two SNPs of ER-α and ER-β to infer frequency of the haplotype alleles present in the population using the program PHASE.[34] For ER-α, the alleles were defined as haplotypes such as "T-A" representing a thymidine (T) nucleotide for the *PvuII* SNP and an adenosine (A) nucleotide for the *XbaI* SNP. We coded ER-α haplotype alleles with numbers 1 through 4 in order of decreasing frequency in the population (1=T-A, 2=C-G, 3=C-A, and 4=T-G).[25, 35] For ER-β, the haplotypes were constructed for the combination of *Intron 2* SNP - *3-prime untranslated region* SNP. In decreasing frequency order, the following haplotypes could be coded: 1=C-C, 2=T-T, 3=T-C, and 4=C-T.[26]

Population for analysis and data analysis

At baseline, 6780 participants (78% of eligibles) underwent an ophthalmologic examination. After excluding persons with prevalent definite or probable OAG (n=221), and those without data on both perimetry and optic disc measures (n=7), 6552 participants formed the cohort at risk for incident OAG.

Data on haplotypes of ER-α was available in 6008 persons and of ER-β in 5826. Analyses on ER-α and ER-β are only presented for haplotype 1 because these were previously reported as risk haplotypes.[25, 35, 36] Analyses on haplotypes 2, 3, and 4 were performed but the results cannot be seen as independent analyses because homozygous carriers of a certain haplotype are among the controls in the analyses of the other haplotypes. The Hardy-Weinberg equilibrium was calculated using Pearson's chi-square analysis.

We used univariate analyses of covariance to compare baseline characteristics of participants and nonparticipants in the follow-up examination, when appropriate adjusted for age and gender. Differences in the distribution of the ER haplotypes were evaluated with Kruskal-Wallis tests. Logistic regression analyses were used to calculate odds ratios with corresponding 95% confidence intervals, which can be interpreted as relative risks. Adding categorical determinants continuously in the model tested statistical significance for trends in increasing exposure. Since estrogens and ERs are thought to have different effects on men and women, we stratified the analyses of ERs on gender, adjusted for age and follow-up time. Analyses were additionally adjusted for the following possible confounders: mean perfusion pressure (defined as ⅔ × diastolic blood pressure + ⅓ × systolic blood pressure – intraocular pressure), body mass index, diabetes mellitus, smoking, total-to-HDL cholesterol ratio, and intraocular pressure lowering treatment. All analyses were performed with SPSS for Windows, version 11 (SPSS Inc., 2001, Chicago, IL).

Results

At baseline, the frequencies of the four possible ER-α haplotype alleles were: 1: 53.3%; 2: 34.8%; 3: 11.9%; and 4: 0%. The frequencies of the four ER-β haplotypes were: 1: 45.1%; 2: 37.0%; 3: 17.2%; and 4: 0.7%. At follow-up, the frequency distributions were similar. The genotype distributions were in Hardy-Weinberg equilibrium.

After a mean follow-up time of 6.5 years (range, 5.0-9.4), 1244 participants had died and 1466 declined or were unable to participate in the follow-up examination, leaving 3842 persons (participation rate, 72%) at risk for incident OAG. Table 7.1 shows baseline characteristics of participants, persons who declined or were unable to participate in the follow-up examination, and deceased persons. Most variables differed significantly between participants and those who refused or died. This did

Table 7.1 Baseline Characteristics of 6552 Persons at Risk for Incident Open-Angle Glaucoma

	Status at Follow-Up		
	Participated (n = 3842)	Declined or Unable (n = 1466)	Died (n = 1244)
Age, y	65.7 ± 6.9	71.2 ± 8.7 ‡	77.4 ± 9.1 ‡
Female gender, %	57.8	68.6 ‡	54.3 ‡
ER-α, haplotype 1 carrier, %	53.1	53.1	54.0
ER-β, haplotype 1 carrier, %	44.3	46.1	46.8
Vertical cup-to-disc ratio*	0.53 ± 0.13	0.50 ± 0.15 ‡	0.48 ± 0.17 ‡
Intraocular pressure, mmHg†	15.1 ± 3.1	15.2 ± 3.4	14.8 ± 3.4
Intraocular pressure lowering treatment, %	1.8	2.7	2.3
Body mass index, kg/m^2	26.3 ± 3.5	26.7 ± 4.0 ‡	25.8 ± 3.9 ‡
Diabetes mellitus, %	6.9	10.6 ‡	20.9 ‡
Systemic hypertension, %	28.9	38.4 ‡	45.5 ‡
Total cholesterol, mmol/l	6.7 ± 1.2	6.7 ± 1.2	6.3 ± 1.3 ‡
HDL cholesterol, mmol/l	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4 ‡
History of stroke, %	1.3	3.5 ‡	7.2 ‡
Demented, %	0.2	3.4	15.2 ‡

Data are unadjusted means ± standard deviation for continuous variables and percentages for dichotomous variables.

* Measured as maximum vertical cup-to-disc ratio of both eyes.

† Measured as maximum intraocular pressure in any of both eyes; persons with intraocular pressure lowering treatment were excluded.

‡ Significant ($P < 0.05$) compared with participants, adjusted for age and gender if applicable.

not hold for the distribution of the ER-α and β haplotypes and most of the OAG-related variables. We detected 87 (2.3%) incident OAG cases at follow-up.

Table 7.2 presents associations between ER-α haplotype 1, ER-β haplotype 1, and incident OAG. We did not find any association for ER-α haplotype 1 and incident OAG. There was an allele-dose dependent increased risk for men, carrying ER-β haplotype 1 ($P = 0.007$), but not in women. Analyses of ER-β haplotype 2 revealed a significant allele-dose dependent inverse relationship ($P = 0.001$) with

incident OAG, again only in men (data not shown). Additional adjustment for other possible confounders had little influence on the relative risk estimates.

Discussion

In this ethnically homogeneous population, we detected a higher risk for incident OAG with ER-β haplotype 1 in men but not in women. The inverse association with ER-β haplotype 2 and incident OAG confirmed the presence of an association between ER-β SNPs and OAG in men. We could not demonstrate any differences in risk of OAG in relation to ER-α genotype.

For confirmation of our findings, we calculated associations between the ER SNPs and prevalent OAG, which should yield the same result because, in theory, genotypes do not change over lifetime. Surprisingly, we found no association for both ER-α and ER-β. A possible explanation for this apparent contradiction is the presence of a prevalence-incidence bias.[37] This bias means that one tends to underestimate the number of cases in cross-sectional studies when the determinant of the disease under study predisposes to shorter survival in patients with this disease. In this study, this would imply that men with OAG carrying ER-β haplotype 1 would have died earlier than similar men without this haplotype. After calculating the mortality risk in persons with prevalent OAG, we indeed found that male OAG cases, carrying ER-β haplotype 1 had a 4.8 times (95% confidence interval, 1.6-14.5, fully adjusted model) higher mortality risk compared to male OAG cases, who did not carry this haplotype.

Different effects of ER-β polymorphisms in men and women were also found studying high blood pressure, low bone mineral density and Alzheimer's disease.[38-40] This strengthens the hypothesis that some effects of ER-β are gender-specific.[27]

Another explanation for the gender difference in OAG, related to ERs, could be the ratio of ER-α to ER-β proteins. With increasing age, the number of ER-α proteins in the retina decreases in women, as measured by reverse-transcription polymerase chain reactions, while in men it stays constant with levels intermediate between young and old female retinas.[23] The number of ER-β proteins in the retina appears to be more constant over age and gender, as measured by these reactions.[24] This leads to different ratios in women but equal ones in men over time. Different ER protein ratios over gender and age have also been found in bone and vascular smooth muscle tissue.[41, 42]

Table 7.2 Associations Between Estrogen Receptor Alpha Haplotype 1, Estrogen Receptor Beta Haplotype 1, and Incident Open-Angle Glaucoma

Estrogen receptor alpha

Allele-copies	*Men* At Risk	Cases	%	Relative Risk (95% confidence interval) Model 1*	Model 2†	*Women* At Risk	Cases	%	Relative Risk (95% confidence interval) Model 1*	Model 2†
0	341	7	2.1	1.00	1.00	467	7	1.5	1.00	1.00
1	763	24	3.1	1.49 (0.63-3.50)	1.31 (0.54-3.15)	1013	26	2.6	1.78 (0.77-4.14)	1.67 (0.71-3.91)
2	452	8	1.8	0.86 (0.31-2.39)	0.58 (0.19-1.78)	580	10	1.7	1.18 (0.44-3.11)	0.98 (0.36-2.69)
Trend				0.86	0.31				0.86	0.87

Estrogen receptor beta

Allele-copies	*Men* At Risk	Cases	%	Relative Risk (95% confidence interval) Model 1*	Model 2†	*Women* At Risk	Cases	%	Relative Risk (95% confidence interval) Model 1*	Model 2†
0	476	7	1.5	1.00	1.00	624	15	2.4	1.00	1.00
1	728	18	2.5	1.72 (0.71-4.16)	1.53 (0.61-3.82)	991	21	2.1	0.89 (0.45-1.73)	0.89 (0.44-1.78)
2	304	16	5.3	3.59 (1.45-8.85)	3.57 (1.38-9.23)	396	7	1.8	0.77 (0.31-1.92)	0.82 (0.33-2.07)
Trend				0.004	0.007				0.57	0.66

* Adjusted for age and follow-up time.

† Adjusted for age, follow-up time, mean perfusion pressure, body mass index, diabetes mellitus, smoking, total-to-HDL cholesterol, intraocular pressure lowering treatment.

We suggest that the risk of OAG depends on the ratio of ER-α to ER-β, with a protective effect of ER-α and a harmful effect of ER-β, and on levels of estrogens. Because premenopausal women have higher levels of estrogens and higher levels of ER-α, their ratio favors protection against OAG, while men have less protection due to lower levels of these. At the moment of menopause, ER-α still predominates, leading to more OAG in women with an early menopause since they have an early depletion of their estrogens. In postmenopausal women, the polymorphisms have little influence because their levels of estrogens are low. Men have higher levels of estrogens at older age compared to women, explaining the polymorphism-related incidence of OAG.[43]

A limitation of our study is the relatively large group of persons who were lost-to-follow-up. The large number of deaths that occurred in this elderly cohort during follow-up can partially explain this. If persons who died between baseline and follow-up developed OAG more often than those who survived, this would have biased the results toward the null value. However, people who have OAG are not at an increased risk of death (except for a possible subgroup of men with ER-β haplotype 1),[44, 45] making bias due to selective death at follow-up less likely. On the other hand, we still find an association despite a possible bias towards the null value. The differences in age will probably have resulted in fewer incident cases, leading to larger confidence intervals in this study, because OAG occurs more often at older ages.

In conclusion, we found an association with ER-β polymorphisms and OAG in men. We could not detect any associations with ER-α or ER-β in women. The exact mechanism why there is a gender difference in OAG has still to be elucidated but a possible pathway might be the ratio of ER-α to ER-β, and levels of estrogens, which changes over time in females.

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8

General Discussion

General Discussion

The aim of this thesis was to determine the incidence of open-angle glaucoma (OAG) and to find risk factors of OAG. We used an epidemiological approach, the Rotterdam Study, to obtain answers to these issues. In this chapter, I will discuss methodological topics related to this approach, present the main findings with their clinical relevance, and provide suggestions for future research.

Methodological issues

Epidemiology is a medical science that studies the frequency of diseases. Prevalence and incidence are two important terms that form the basis of epidemiological research. Prevalence is the number of diseased persons in a group at a certain moment in time. Incidence is the number of diseased persons that emerge from a healthy population in a defined time period.

Possible risk factors can be investigated with several study designs. We have chosen for an observational, population-based, longitudinal, closed cohort study design. This means that we selected a population (all people aged 55 years or older), in a particular area (living in Ommoord, a district of Rotterdam), at a certain time (spring 1989) with no other restrictions, and followed this cohort prospectively in time.[1] No experimental interventions took place and no persons were added during the follow-up period of this OAG study.

The advantage of a population-based design instead of a clinic-based design is the reduction in selection bias, which can occur in clinic-based studies due to distortion by determinants related to the disease. The longitudinal, prospective scheme provides the opportunity to calculate directly incidences instead of deriving them from prevalence data with formulas. Furthermore, with this time window, it is easier to determine the cause – consequence chain, which is important for defining risk factors. A fourth benefit of our study design is the limited role for information bias since the assessment of risk factors takes place before the onset of the disease.

Incidence can be expressed in two terms: cumulative incidence and incidence rate. The difference between these two is the population in the denominator. For cumulative incidence, all persons at risk for the disease at the beginning of the study form the denominator. The denominator of the incidence rate is the total amount of person-years during follow-up instead of persons. One person-year is equal to

a follow-up time of one year of one person, but it can also be, for example, two persons with each having a half-year of follow-up time. When the follow-up time is not equal for all participants and there is a considerable loss to follow-up, both are applicable to the Rotterdam Study, the incidence rate provides a better estimate of the incidence than cumulative incidence. With an exponential formula, the incidence rate can be transformed into cumulative incidence,[2] which is easier to interpret since it is an absolute risk to get diseased in a certain time period.

In search of risk factors, one should always consider the precision and validity of the study results. Precision involves the reproducibility of the measurements or the lack of random error. A larger size of examined groups will give a higher precision of the estimates with smaller confidence intervals. This could be a problem for incident OAG in the Rotterdam Study because we only had 29 cases with incident definite and 58 cases with incident probable OAG. Another aspect of precision is the variation in the measurement itself. This is particularly applicable in our study for the semi-automated optic disc measurements, retinal vessel measurements and intraocular pressure readings. Within- and between-grader variability was therefore regularly tested, and had good to excellent results.[3-5]

Validity involves the reflection of the reality or the lack of systematic error. It can be subdivided in external and internal validity. External validity deals with the question if the results of this study can be extrapolated to other populations. The reader of the article is the only person who can give the answer to this question. Internal validity has to do with the correctness of the results of the studied population. Three aspects of internal validity are: selection bias, information bias and confounding.

Selection bias occurs when the relation between the determinant and the outcome is different for those who participate and those who do not participate. If persons with high exposure and high risk of the disease refuse to participate, selection bias is introduced. The high participation rates in the Rotterdam Study will reduce the possibility of selection bias.[6,7] Loss to follow-up is another form of selection bias. This is particularly important in the Rotterdam Study because for its ophthalmic part we only use data obtained during center visits. Monitoring through medical files of ophthalmologists would not give enough detailed information for our diagnosis of OAG and, moreover, not every person visits an ophthalmologist regularly for a general check-up. Nonresponders had different baseline characteristics compared with participants, but this did not hold for glaucoma-related variables such as intraocular pressure and vertical cup-to-disc ratio. Together with the concept that

OAG initially develops without symptoms, we think the role for selective nonresponse was limited in the Rotterdam Study.

Information bias may occur when the determinant or outcome is misclassified, either nondifferential or differential. Nondifferential or random misclassification generally results in weakening of the associations. The standardized procedures of evaluating glaucomatous visual field loss and optic disc neuropathy reduce the potential for nondifferential misclassification in the Rotterdam Study. Differential or nonrandom misclassification occurs in follow-up studies when the assessment of the disease in the exposed differs from the assessment in the non-exposed. This can lead to either overestimation or underestimation of the true association. The prospective design of the Rotterdam Study excludes the possibility of differential misclassification of the determinants because the status of incident OAG was not known at baseline. Differential misclassification of OAG in our study was also unlikely, because we used semi-automated measurements and investigators were masked for the determinants when assessing the diagnosis of OAG.

Confounding may be considered a confusion of effects. A potential confounding factor is both related to the determinant and, independent of the determinant, to the outcome, but does not take part as an intermediate in the causal pathway. A way to deal with confounding in observational cohort studies is to measure the effect of a confounder carefully and subsequently adjust for it in the analyses. Even though I adjusted for several potential confounders, the possibility of insufficient measurements of confounders (residual confounding) or the presence of unknown confounders should always be considered in observational studies.

Main findings with their clinical relevance

Incidence of visual field loss

We detected 175 persons who had developed visual field loss during follow-up. The 5-year cumulative incidence increased significantly with age from 1.9% for persons aged 55 to 59 years, to 10.0% for persons aged 80 years or older. Men had a higher risk of developing visual field loss than women. Open-angle glaucoma was the main cause, followed by stroke and age-related macular degeneration. We also calculated the 5-year cumulative incidence of glaucomatous visual field loss. This increased significantly from 0.4% at age 55 to 64 years, to 2.0% at age 75 years or older. This is the first population-based study providing data on incident

visual field loss and its causes. A normal visual field is important for the elderly to remain independent.[8] Without it, walking and driving becomes more difficult.[9-11] For prevention and detection strategies, incidence data are necessary to estimate the frequency of future screening programs. As part of the diagnosis OAG, data on incident glaucomatous visual field loss are essential as well. In our study, we used an automated screening test on all participants and performed manual Goldmann perimetry as a confirmative test in those with positive or unreliable results. Problems in comparison with other future studies could arise because kinetic Goldmann perimetry as gold standard was replaced by automated perimetry in the past decade. That is why at follow-up we performed, for comparative purposes, both kinetic Goldmann perimetry and automated Humphrey Central 24-2 full-threshold perimetry for confirmation of screening defects. Automated perimetry is less dependent on the skills of the perimetrist, but is found to be more tiring, giving less reliable results, in older patients.[12-14] New techniques, such as frequency doubling perimetry and high pass resolution perimetry, and new algorithms, such as Swedish interactive thresholding algorithm and tendency-oriented perimetry, have been developed to overcome this problem.[15, 16]

Incidence of open-angle glaucoma

Many population-based cohort studies on prevalent OAG have been described, but only few have published on incident OAG.[17-20] We diagnosed 29 participants with incident definite OAG and 58 with incident probable OAG. Combined, the 5-year cumulative incidence increased significantly from 1.4% in persons aged 55 to 59 years, to 2.6% in persons aged 80 years or older. There was a tendency for higher risk in men, but this was not statistically significant. Most of the cases were unaware of having OAG. We also found a fivefold increased risk for healthy fellow-eyes in persons with unilateral prevalent OAG. These results emphasize the importance of improving the detection of OAG with increasing age and the need for a regular check-up of both eyes in patients with unilateral OAG. Our results did not show a clear gender difference compared to our baseline analysis, but this does not mean there is no such relationship. If the relationship is less obvious, many incident cases are needed to detect the difference, which we lack in our study.

Retinal vessel measurements

In cross-sectional studies, OAG has been associated with narrowing of arterioles or venules,[21-23] which is an indication of the involvement of the vascular system.[24]

However, this finding does not answer the question whether an impaired circulation plays a causative role in the pathophysiology of OAG or occurs as a consequence of OAG. In our study, we could not detect an association with retinal vessel diameters and incident OAG or glaucomatous optic disc changes. This implies that there is no retinal vascular role in the pathogenesis of OAG. Changes in the diameters of the short posterior ciliary arteries, which are responsible for the blood supply to the optic nerve head,[25] have not been investigated and might still be involved in the vascular hypothesis.

Diabetes mellitus

Diabetes mellitus is an unsettled risk factor of OAG. Cross-sectional studies resulted in controversial findings,[26-29] while two studies with incident OAG showed no association.[30,31] We were unable to find an association between diabetes mellitus and incident OAG in the Rotterdam Study. A limitation of our analysis was the low number of cases with OAG among the participants with diabetes mellitus. This resulted in large confidence intervals, with the possibility that a small effect of diabetes mellitus may have been missed now. Based on our results and the other two incidence studies, we conclude that patients with diabetes mellitus are no longer at high risk for OAG, in contrast to previous opinions.[32, 33]

Atherosclerosis

Besides the mechanical theory, a vascular one has been proposed on the pathophysiology of OAG,[24, 34, 35] as mentioned earlier. Impaired perfusion of the optic nerve head could lead to ischemia and consequently to the death of retinal ganglion cells with their axons. Atherosclerosis is one way to cause impaired perfusion. We could not find any associations with several measures of generalized atherosclerosis. Neither did we find a relationship with C-reactive protein levels, which are closely related to the amount of atherosclerosis. This means that generalized atherosclerosis and inflammation do not play a part in the vascular pathophysiology of OAG. Again, localized atherosclerosis in the short posterior ciliary arteries has not been measured. If the process of atherosclerosis formation in these arteries is distinct from the processes in the larger vessels, this might play a role in impaired perfusion. For clinical practice, this means that the risk of OAG cannot be deduced from measures correlated to generalized atherosclerosis.

Estrogen receptor alpha and beta

Estrogen levels before and after the menopause and the use of hormone-replacement therapy have been associated with OAG,[36, 37] although other studies refute this.[38, 39] The effect of estrogen is accomplished through two receptors, both available in men and women. We examined the influence of two polymorphisms in each of the two genes of these receptors on the risk of OAG. In women, we found no association between all four polymorphisms and incident OAG. In men, however, we discovered an increased risk of incident OAG in carriers of estrogen receptor beta haplotype 1. Estrogen receptor alpha polymorphisms showed no associations in men. The clinical relevance of this finding is less obvious at this time.

Suggestions for future research

The research in this thesis was based on a limited number of incident OAG cases. This resulted in estimates with large confidence intervals, making it difficult to find small associations. Open-angle glaucoma is a multifactorial disease, where more minor associations are likely to play a role than a few large predictors. Therefore, we must track down more cases with incident OAG to obtain estimates with a larger precision in the future. Two methods to accomplish this are already implemented in the Rotterdam Study: extension of the follow-up period and inclusion of more persons to the cohort.

Another way to obtain better estimates is by means of pooling data. Across the world, two large population-based studies have gathered information on incident OAG and other population-based studies might still be on their way. Although we have to overcome the problem of different definitions of OAG and consider possible differences in the data collection, this can be a valuable exercise leading to improved results.

Early detection of glaucomatous changes in the optic nerve head becomes more and more important because glaucomatous visual field loss is considered to be a late phase of OAG. Computerized measurements have the advantage of easy comparison of images over time compared to ophthalmoscopic evaluation. In our study we used a semi-automated image analyzer, which is not commercially available anymore. New computerized methods have appeared to detect glaucomatous changes in the optic disc such as confocal scanning laser tomography,[40] optical coherence tomography,[41] and scanning laser polarimetry,[42] with similar detection

results.[43] We use now both the confocal scanning laser tomograph and the ImageNet analyzer in the Rotterdam Study, which turn out to correlate well.[44] Future analyses of risk factors will focus more on the early optic disc changes rather than on late stage OAG with visual field loss.

In what direction should we continue for unraveling the etiology of OAG? Unhealthy life style factors are associated with many diseases. The relatively easy way to change these factors makes them an interesting subject of study. Smoking,[45, 46] alcohol consumption,[47, 48] obesity,[28, 49] lipid levels,[50-52] hypertension,[53, 54] and coffee consumption[55, 56] are still disputable risk factors for OAG, so advanced research is necessary.

Another direction for future research is exploration of the vascular dysregulation, oxidative stress involvement, and excitotoxic mechanisms. This can be done in several areas, such as symptoms of patients,[57, 58] concentration of substances,[59-61] medication use,[62-64] or DNA configuration.[65] Other interesting topics are the influence of thyroid hormones,[66-68] infection with Helicobacter pylori or other pathogens,[69, 70] alterations in the immune system,[71, 72] changes in the extracellular matrix,[73-75] and the effect of systemic medication use.[76-78] Also, exploration of gene mutations in patients with OAG is becoming increasingly popular.[79-82]

In conclusion, although the disease of OAG is known for centuries, only a few risk factors have been securely established by now. Other potential risk factors and possible pathways need further investigation.

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9

SUMMARY

Primary open-angle glaucoma (OAG) is an eye disease, characterized by loss of retinal ganglion cells and their axons. Clinically, this loss becomes apparent by cupping, also called excavation, of the optic disc and concomitant visual field loss. Despite the fact that this disease is known for centuries, little is known about its etiology. The aim of this thesis was to provide data on the incidence of primary OAG and to find risk factors for this disease.

We used data from the Rotterdam Study in all our analyses to obtain answers to these questions. The Rotterdam Study is a prospective, population-based cohort study among 7983 persons aged 55 years and older, living in a district of Rotterdam, the Netherlands. It focuses on the frequency and determinants of the most invalidating and common cardiovascular, locomotor, neurological, and ophthalmic diseases in the older community. Baseline examinations took place from 1990 to 1993, and the follow-up examinations for primary OAG were performed from 1997 to 1999. Since OAG cases with pseudoexfoliation were not specifically excluded at baseline, we prefer to refer to OAG instead of primary OAG although during follow-up, no pseudoexfoliation was observed.

We first calculated the incidence of visual field loss and examined its causes in Chapter 2. The incidence increased significantly with age and was higher in men than in women. The leading cause in all age groups was OAG, followed by stroke and ageing macular disease.

In Chapter 3, we described the incidence of OAG, which increased significantly with age as well. Gender seemed not to be related to incident OAG. The low number of incident cases could explain this finding that is different from the higher prevalence of OAG in men. Another striking finding was the increased risk of OAG for the second eye of a person with unilateral OAG compared with the risk of two healthy eyes. Most patients with incident OAG were unaware of having this disease.

Next, we investigated some possible risk factors, starting with the diameter of retinal blood vessels in Chapter 4. We could not find an association between arteriolar or venular retinal vessel diameters and incident OAG, nor with changes in the optic disc, such as the width of the neural rim. This means that an impaired retinal circulation probably does not play a role in the pathogenesis of OAG.

In Chapters 5 and 6, we examined disorders as diabetes mellitus and atherosclerosis as possible risk factors for OAG. Although diabetes mellitus was thought to be a risk factor of OAG, we could not confirm this. We used generalized atherosclerosis as an indicator for decreased blood flow in the optic nerve head, and

were unable to detect an association between severe atherosclerosis and incident OAG.

Finally, polymorphisms, or common DNA sequence variations, in the estrogen receptors were investigated in Chapter 7. Variations in the estrogen receptor alpha did not lead to a higher risk of OAG in both men and women. On the other hand, certain alterations in the estrogen receptor beta led to a higher risk of incident OAG in men, but not in women.

In Chapter 8, the main findings of the studies described in this thesis were discussed, together with some methodological considerations of the Rotterdam Study. Suggestions for future research were also provided in this chapter.

10

SAMENVATTING

Primair open-kamerhoek glaucoom is een oogziekte, die wordt gekarakteriseerd door het verlies van zenuwcellen in het netvlies met hun bijbehorende uitlopers. Dit verlies van zenuwvezels uit zich in de praktijk door middel van uitholling van de oogzenuw en het daarmee gepaard gaande gezichtsveldverlies. Hoewel deze ziekte al vele eeuwen bekend is, weten we nog maar weinig over de oorzaken van glaucoom. Het doel van dit proefschrift bestond uit twee delen: enerzijds het verschaffen van informatie over het aantal nieuwe patiënten met open-kamerhoek glaucoom dat optreedt gedurende een bepaalde tijdsperiode (ook wel incidentie genoemd), anderzijds om eigenschappen te vinden die deze incidentie van glaucoom kunnen beïnvloeden.

In al onze berekeningen hebben we gegevens gebruikt van het Erasmus Rotterdam Gezondheid & Ouderen (ERGO) onderzoek om antwoorden te vinden op bovenstaande vragen. Het ERGO-onderzoek is een lopend onderzoek onder een groep mensen uit de algemene bevolking van 55 jaar en ouder die in een bepaalde wijk van Rotterdam wonen. Het onderzoek richt zich op de frequentie en risicofactoren van de meest invaliderende ziekten van het hart- en vaatstelsel, bewegingsapparaat, zenuwstelsel en de ogen op oudere leeftijd. De eerste onderzoeksronde vond plaats van 1990 tot 1993. Het vervolgonderzoek voor incident open-kamerhoek glaucoom werd uitgevoerd van 1997 tot 1999.

Omdat patiënten met open-kamerhoek glaucoom op basis van pseudo-exfoliatie niet specifiek werden uitgesloten tijdens de eerste onderzoeksronde, spreken wij liever van open-kamerhoek glaucoom in plaats van primair open-kamerhoek glaucoom, ook al hebben we tijdens het vervolgonderzoek geen pseudoexfoliatie meer waargenomen.

Allereerst berekenden we in hoofdstuk 2 de incidentie van algemeen gezichtsveldverlies met de daarbij horende oorzaken. De incidentie steeg aanzienlijk met toename van de leeftijd en was hoger voor mannen dan voor vrouwen. De voornaamste oorzaak voor gezichtsveldverlies in alle leeftijdscategorieën was open-kamerhoek glaucoom, gevolgd door beroertes en ouderdomsslijtage van het netvlies.

In hoofdstuk 3 beschreven we de incidentie van open-kamerhoek glaucoom, welke eveneens sterk steeg met toename van de leeftijd. Verschillen in geslacht leken niet gerelateerd te zijn aan incident glaucoom, maar door het lage aantal patiënten met glaucoom was dit niet met zekerheid te zeggen. Een andere bevinding was het verhoogde risico op open-kamerhoek glaucoom in het tweede oog bij personen die reeds in één oog open-kamerhoek glaucoom hadden, ten opzichte van personen

die aanvankelijk twee gezonde ogen hadden. Het merendeel van de patiënten met incident open-kamerhoek glaucoom was niet op de hoogte dat zij deze ziekte hadden ten tijde van ons onderzoek.

Vervolgens hebben we enkele mogelijke risicofactoren onderzocht. In hoofdstuk 4 keken we naar de doorsnede van de bloedvaten in het netvlies. We vonden geen verband tussen zowel de doorsnede van de slagaders als de aders van het netvlies en het optreden van incident open-kamerhoek glaucoom. De doorsnede van de bloedvaten was geen indicatie voor meetkundige veranderingen in de oogzenuw na enkele jaren. Dit betekent dat een afwijkende bloedsomloop in het netvlies waarschijnlijk geen rol speelt in het ontstaan van open-kamerhoek glaucoom.

In de hoofdstukken 5 en 6 bestudeerden we de mogelijk ongunstige invloeden van ziektebeelden zoals suikerziekte en aderverkalking op het ontstaan van open-kamerhoek glaucoom. Men was van mening dat het hebben van suikerziekte een risicofactor was voor open-kamerhoek glaucoom, maar dit konden wij in ons onderzoek niet bevestigen. We gebruikten de mate van aderverkalking in enkele grotere slagaders als een aanwijzing voor de mate van verminderde bloedsomloop ter hoogte van de oogzenuw. We konden geen relatie aantonen tussen ernstige aderverkalking en het optreden van open-kamerhoek glaucoom.

Tot slot onderzochten we in hoofdstuk 7 de invloed van kleine veranderingen in het DNA van twee eiwitten, betrokken bij de signaaloverdracht van het hormoon oestrogeen. Variaties in het eerste eiwit (oestrogeen receptor alpha) leidden niet tot een verhoogde kans op het krijgen van open-kamerhoek glaucoom in zowel mannen als vrouwen. Echter, veranderingen in het tweede eiwit (oestrogeen receptor beta) bleken wel te leiden tot een verhoogd risico voor mannen, maar niet voor vrouwen, op het ontstaan van open-kamerhoek glaucoom.

De belangrijkste bevindingen van de beschreven onderzoeken in dit proefschrift, bespraken we in hoofdstuk 8, samen met de methodologische overwegingen gerelateerd aan het ERGO-onderzoek. Tevens opperden we enkele ideeën voor toekomstig onderzoek naar risicofactoren van open-kamerhoek glaucoom.

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Simone

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Simone de Voogd was born on February 25th, 1976 in Leidschendam, The Netherlands. She graduated in 1994 at the Thomas à Kempis College in Arnhem. From 1994 to 1995, she studied Pharmacy at the University of Utrecht, where she passed her propaedeutic exam. In September 1995, she started to study Medicine at the Erasmus University Rotterdam. During medical school, she organized lectures and symposia for Capita Selecta and participated in an exchange program at the Institute of Cardiovascular Diseases (prof.dr. D. Stojšic) in Sremska Kamenica, Yugoslavia. She obtained her medical degree in January 2002. After a short period working as a resident in Internal Medicine at the IJsselland Hospital (dr. H.R.A. Fischer), she started the work described in this thesis in August 2002 under supervision of prof. dr. P.T.V.M. de Jong and prof.dr. A. Hofman at the Department of Epidemiology and Biostatistics of the Erasmus Medical Center, Rotterdam. In 2004, she obtained a Master of Science degree in Clinical Epidemiology from the Netherlands Institute for Health Sciences in Rotterdam. On April 1st, 2006, she will start her residency in Ophthalmology at the Department of Ophthalmology of University Medical Center Utrecht, headed by prof.dr. J.S. Stilma.