ARTICLE ORIGINAL

Systemic risk factors underlying primary open-angle glaucoma

Facteurs de risque systémiques du glaucome primitif à angle ouvert.

Khallouli Asma, Oueslati Yassin*, Bouchoucha Saker, Gouider Dhouha, Maalej Afef, Rannen Riadh.

Department of Ophthalmology, Military Hospital of Tunis, Tunisia
Faculty of Medicine, University of Tunis El Manar, Tunis, Tunisia.

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Risk factors, primary open-angle glaucoma.

Abstract

Purpose. To analyze the epidemiological profile of primary open-angle glaucoma (POAG) in a sample of 119 patients (209 eyes) with different stages of glaucoma and identify systemic risk factors associated with its progression.
Methods. A retrospective descriptive study, involving 209 eyes of 119 subjects, over a period of 2 years. The data was collected from medical records. Analysis focused on the study of systemic risk factors.
Results. The mean age of the manifest glaucomatous patients was 62.48 +/- 14.45 years. The sex-ratio was 1.23 (M / F). Most common risk factors were hypertension (42.9%), diabetes (25.2%), tobacco (27.7%) and dyslipidemia (23.5%). Blood hypertension and coronary artery disease presented the greatest odds ratios, 3.8 and 3.23 respectively. Risk factors distribution according to severity stage showed that hypertension remains the most important risk factor, regardless the disease severity.
Conclusions. POAG is a common multifactorial disease. Identifying and suppressing, when possible, the associated risk factors should represent a significant time in therapeutic management. These facts will allow maximizing the advantage of lowering intraocular pressure (IOP) which remains until now the only possible therapeutic option.

Introduction

Glaucoma is currently the third blindness cause in the world, it is a chronic optic neuropathy characterized by progressive loss of retinal ganglion cells and optic nerve fibers, associated with a painless and insidious perimetric deficit.
Glaucoma has benefited from considerable progress over the past decade in terms of diagnosis, follow-up and therapeutic care. Indeed, in some cases and despite good intraocular pressure (IOP) control, the neuropathy continues to progress on its own account, involving the functional prognosis of the patient.
Several studies have shown that primary open-angle glaucoma (POAG) is a multifactorial pathology, which progression is related to multiple local and systemic risk factors varying from one population to another.
Thus, identification of POAG development predictive factors among patients is essential, in order to isolate subjects at risk and to adapt therapeutic management.

Methods

Study Design and Patient Recruitment

The study involved 209 eyes of 119 subjects: 51 eyes from 32 patients followed for preperimetric glaucoma, and 158 eyes from 87 patients followed for perimetric POAG, divided into 3 groups according to mean deviation's value (MD): early glaucoma (MD>-6dB), moderate glaucoma [-6 to-12 dB [and advanced glaucoma (MD≤ 12 dB).
All patients included in the study underwent a complete bilateral ophthalmologic examination.
Data were collected retrospectively from patient medical records, including age, gender, presence or absence of glaucoma family history, blood hypertension, diabetes, dyslipidemia, coronary artery disease, vasospastic disorders (migraine, Raynaud), smoking. Inclusion criteria for manifest glaucoma group were: Open iridocorneal angle, glaucomatous changes of optic disc, retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) defect on spectral-domain OCT, consistent glaucomatous pattern on visual field examinations.
For preperimetric glaucoma group, subjects were required to have; age> 40 years old, glaucomatous structural findings as stated above in criteria for perimetric glaucomatous eyes, and normal VF results.
Exclusion criteria were as follows: history of eye surgery (other than uncomplicated phacoemulsification cataract surgery), Presence of ophthalmological or other pathologies responsible for impaired vision or visual field, narrow iridocorneal angle and all other forms of secondary open-angle glaucoma (post-traumatic, post uveitis...).

Statistical Analysis

Distribution's normality for numerical data were tested by the Kolmogorov-Smirnov test.
The comparative study of means was carried out by the student's test in the case of normal distribution, otherwise the non-parametric Mann-Whitney test was used.
The effect of risk factors was assessed by calculating odds ratios:
- OR = 1 no association between evaluated factor and POAG
- OR> 1 the analyzed factor represents a risk of POAG occurrence
- OR <1 the studied factor has a protective role

All statistical analyses were performed with IBM® SPSS® Statistics 23.0 software and Excel Microsoft Office 2016.

Results

A total of 209 eyes from 119 patients were included (**Table I**). For each group, we included only eyes meeting the criteria mentioned above.

*Corresponding author :
Yassin Oueslati
Email: weslatiyassin10@gmail.com
Department of Ophthalmology, Military Hospital of Tunis, Tunisia

Age distribution

For perimetric glaucoma group, the mean age was 62.48 +/- 14.45 years, higher than preperimetric glaucoma group 53.29 +/- 9.43 years (p <0.01). Relative risk was 1.42 for an age > 50 years. The odds ratios were 3.23, 95% CI (1.75-5.96) for an age between [50-59 years] and 3.61, 95% CI (1.93-6.75) for an age between [60-69 years]. There was no significant difference between the ages of men and women (p> 0.05).

Table I. Number of patients and eyes included in the study.

	Number of patients	Number of eyes
Preperimetric glaucoma	32	51
Manifest glaucoma	87	158
Total	119	209

Gender distribution

The number of men included in the study was greater than women; (56.3%) male and (43.7%) female; sex ratio (male / female) was 1.28 (**Table II**).

Table II. Gender Distribution.

	Men	Women
Preperimetric glaucoma	20	12
Manifest glaucoma	47	40
Total	67	52

Distribution by stage of glaucoma

Of the 209 glaucomatous eyes included in the study, we can distinguish; 51 eyes (24.41%) had preperimetric glaucoma, 69 eyes (33.01%) had an early glaucoma, 44 eyes (21.05%) had a moderate glaucoma, and 45 eyes (21.53%) had an advanced glaucoma (**Figure 1**).

Patients' general history

High blood pressure (hypertension) was the most common risk factor (42.9%) with an odds ratio of 3.801 [1.493-9.676], followed by, in descending order; tobacco (27.7%), diabetes (25.2%), dyslipidemia (23.5%), coronary artery disease (14.3%), family history of glaucoma (13.4%) and vasospastic disorders (7.6%).
The limited number of patients presenting a vasospastic disorder or having family history of glaucoma explains the low values of the observed odds ratios (**Table III**).
The study of risk factors distribution according to glaucoma severity stages had shown that blood hypertension was the most important risk factor regardless disease severity (**Figure 2**).
Likewise, diabetes, coronary artery disease and dyslipidemia had also a growing incidence, increasing with disease progression.

Discussion

In our study, the mean age of glaucomatous patients was 61.69 +/- 14.56 years. Relative risk was 1.42 for an age > 50 years.

Similar results have been observed in the literature; the Barbados Eye Study, demonstrated an odds ratio of 1.4 and 2.3 respectively for age groups between (50-59 years) and (60-69 years). The risk of glaucoma is multiplied by 1.04 for each year of age [1]. The association between POAG and age is explained by the action of epigenetic factors, involved in the regulation of some genomic region responsible for normal development, aging as well as for the course of many chronic neurodegenerative diseases [2].

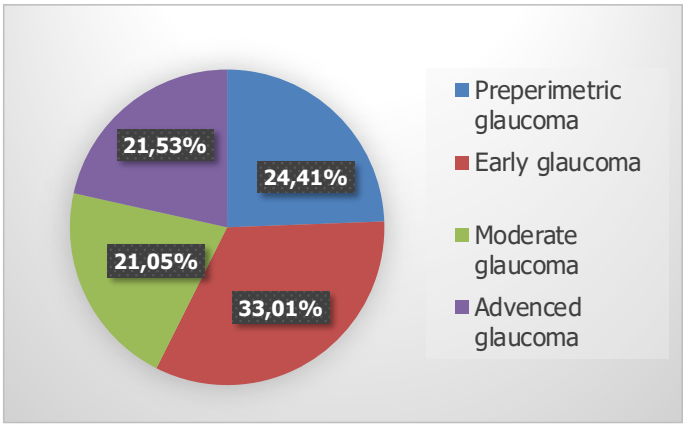

Figure 1. Distribution of glaucomatous patients according to the stage of glaucoma.

Likewise, it has been proven that prevalence and evolutionary profile of glaucomatous disease vary according to ethnicity. All subjects included in our study were Caucasian from North Africa. The prevalence is slightly higher in our population compared to European and American populations. These results are explained by a thinner cornea, a larger optic disc and a thinner layer of retinal nerve fibers [3,4]. It is also explained by differences in socioeconomic, geographical and also cultural factors making the diagnosis of POAG later and therefore responsible for a delay in therapeutic management, which worsens the visual prognosis [5].

Table III. General history and odds ratio.

	Percent (%)	OR
Blood hypertension	42,9	3,801 (1,493-9,676)
Diabetes	25,2	2,605 (0,826-8,219)
Coronary artery disease	14,3	3,229 (0,696-14,977)
Dyslipidemia	23,5	2,605 (0,826-8,219)
Vasospastic dis-orders	7,6	0,741 (0,174-3,151)
Tobacco	27,7	1,415 (0,543-3,688)
Family history of glaucoma	13,4	0,594 (0,211-1,670)

Male gender has been considered as a high-risk factor for POAG, however this notion remains controversial. In our study, the prevalence of men (55.3%) was slightly higher than women (44.7%). In many publications, no significant association between gender and risk of POAG development was found [6]. On the contrary, in the Barbados Eye Study, the risk of developing POAG in men was multiplied by a factor of 1.31 [1]. The lack of statistically significant difference in some publications like ours can be explained by the limited number of subjects included in the study.
Besides, the prevalence between two sexes depends on ethnic

factors as well as inclusion criteria adopted in each study. However, given the strong correlation between age and POAG and the fact that women have a higher life expectancy than me, even a small difference in the statistical methodology and age distribution in the studied sample can be source of results disparity [6].
In the studied cohort, 14.38% of patients reported a family history of glaucoma. The increased risk of developing POAG in individuals with glaucomatous parents as well as in monozygotic twins suggests the notion of an inherited risk factor in POAG [4]. Thus, the Baltimore Eye Survey reported a higher risk, in descending order; among siblings, parents and then children with an odds ratio, respectively: 3.69-2.17-1.12 [7]. The most frequent mutations involve the gene (GLC1A) on chromosome 1 encoding for myocilin, found in 4.1% of glaucomatous subjects [8].
For several authors, diabetes predisposes to POAG. However, results in the literature are still controversial. In our study, 21.23% of patients were diabetic. In other studies, the risk of developing POAG was higher in diabetic patients: 2 to 3 times higher than in non-diabetics [9,10].
These facts are explained as being the result of diabetic microangiopathy, directly affecting the vascularization of the optic nerve head [11]. Furthermore, diabetes is responsible for glucose level increase in the aqueous humor, thereby stimulating the production of fibronectin and its accumulation in the trabecular mesh work [12]. For others, it is the glycosylation of extracellular proteins of the trabecular matrix that is responsible for the reduction of aqueous humor outflow [13]. Likewise, diabetic patients tend to have a regular ophthalmologic examination compared to non-diabetic subjects, which can explain the increased incidence of POAG observed in our population [14].
High blood pressure has been observed in 45.89% of patients with an odds ratio: 2.75, 95% CI [1.43-5.3]. This prevalence increases with the severity of glaucoma stage. Hypertension acts initially by increasing the blood flow and therefore helps to counteract the effect of IOP. However, in long term it may increase peripheral vascular resistance through atherosclerosis and loss of local self-regulation aggravated by age. All these mechanisms are responsible for a chronic hypoperfusion of optic nerve head, and

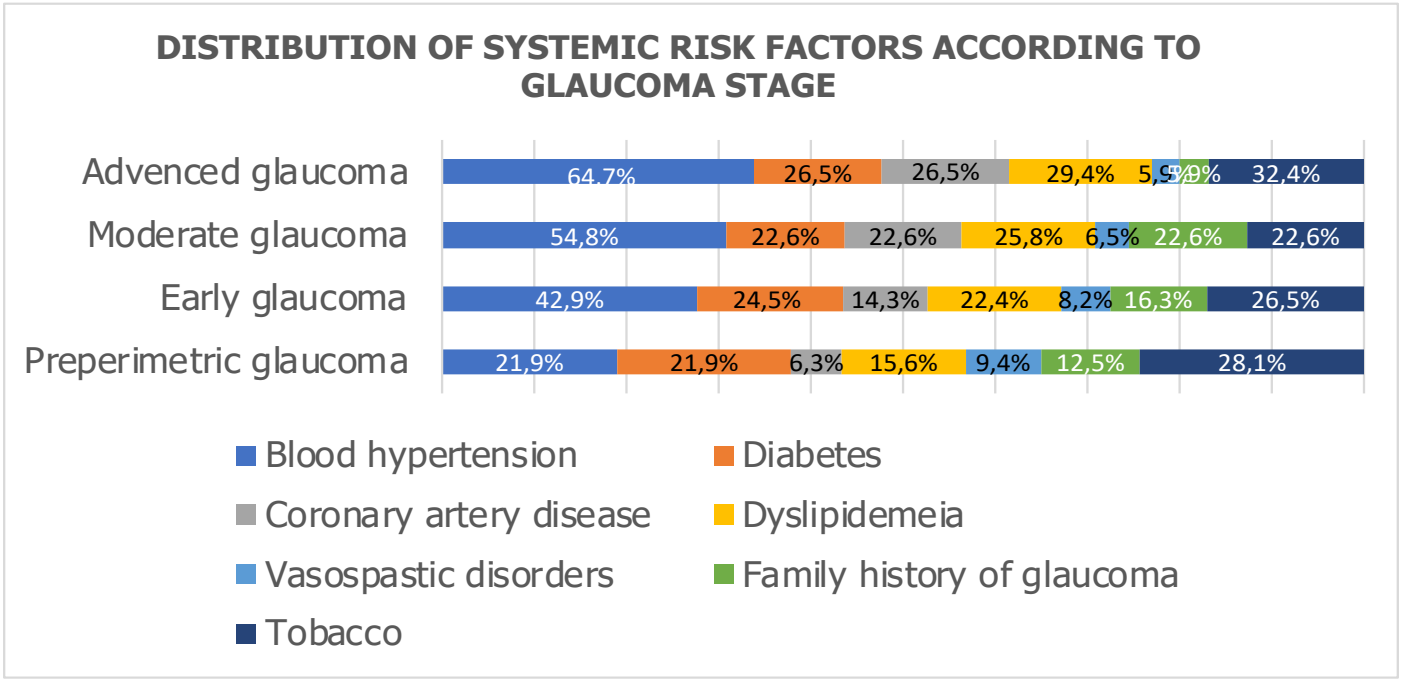

Figure 2. **Systemic risk factors according to glaucoma stage.**

so aggravating glaucoma progression [10,15]. A history of coronary artery disease was observed in 15.75% of patients, the odds ratio was 2.5, 95% CI [0.84 - 7.4]. Similarly, it was found that prevalence of coronary artery disease and cardiovascular pathologies was higher in glaucomatous patients (20%) than in general population (17%) [16]. It is important to note that, the role of coronary artery disease must be analyzed while considering that coronary disease is the result of several pathological conditions (hypertension, dyslipidemia, diabetes, etc.). Hence, the difficulty in assessing the specific accountability of this parameter in the development of glaucomatous pathology.
The role of dyslipidemia remains controversial. In our study, dyslipidemia was noted in 23.28%. The Beijing Eye Study showed that prevalence of glaucoma between dyslipidemic and non-dyslipidemic patients was similar, with no statically significant difference ($p = 0.99$). However, the same study showed that dyslipidemia is associated with an increased IOP ($p < 0.001$) [17]. These facts are explained by blood viscosity increase, responsible for the elevation of episcleral venous pressure, which decreases the outflow of aqueous humor [18].
In our work, a vasospastic disorder (migraine or Raynaud's syndrome) was observed in 7.53% of patients. Functional vasospasm has been significantly correlated with the development and glaucoma progression in several publications. In fact, vasospasm acts directly by increasing peripheral vascular resistance in the choroidal network and consequently reducing the flow of ocular perfusion. This causes a sectoral alteration of the optic nerve head, which is often pale and poorly perfused [19].
Prevalence of smoking was estimated at 27.4%. The role of tobacco in POAG development remains controversial, given the disparity of observed results. The risk of glaucoma was 3.87; 95% CI [1.41-10.59], in heavy smokers, greater than 40 pack-years [20]. Tobacco acts by promoting the onset of peripheral spasms as well as by increasing hematocrit and therefore blood viscosity [21]. Likewise, tobacco represents a ground for the development of other pathological conditions compromising ocular vascularization such as; arteriosclerosis and hypertension [22,23]. Thus, makes difficult to interpret its accountability.

Ethics and conflicts of interest

We declare that we have no conflicts of interest in relation to this study.

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