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Is atrial fibrillation a risk factor for normal-tension glaucoma?

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Abstract

Glaucoma (GL) and atrial fibrillation (AF) are diseases of significant social importance. Cardiovascular disorders such as systemic hypertension, hypotension, increased blood viscosity, vasospasm, and diabetes are potential risk factors of GL, especially when intraocular pressure is not elevated. Only a few studies have reported a possible connection between cardiac arrhythmias and GL. The purpose of this study was to evaluate the risk of GL in patients with AF.

A total of 117 patients were included in the study, 79 with AF (AF group) and 38 with sinus rhythm (Control group), matched for age and sex. The mean ± standard deviation age was 73.6 ± 7.2 and 71.6 ± 4.7 years for the AF and control groups, respectively. There were no statistically significant differences in the percentage of systemic hypertension, congestive heart failure, diabetes mellitus type 2, or vascular disease between the groups. Patients were examined for the presence of normal-tension glaucoma (NTG) by an ophthalmologist.

NTG was confirmed in 40 patients (34.2%) in the entire group, with 35 (44.3%) in the AF group and 5 (13.15%) in the Control group. The incidence of NTG was significantly higher in the AF group ($P = .0221$). Women represented 60% of GL patients in the AF group and 80% in the control group. There were no significant differences in intraocular pressure between the groups (mean ± standard deviation, 14.3 ± 2.3 vs. 14.2 ± 2.8 mmHg, $P = .4202$). Approximately three-fourths of patients with AF and NTG had early visual field damage based on the Hodapp classification.

AF, independent of other known cardiovascular risk factors, increases the risk of developing NTG. Many AF patients do not have conspicuous symptoms of GL, so understanding the possible risk of its development is critical because early detection might help to prevent later visual impairment and even irreversible blindness.

Abbreviations: 95% CI = 95% confidential interval, AF = atrial fibrillation, AION = anterior ischemic optic neuropathy, BCVA = best corrected visual acuity, c/d = vertical cup to disc ratio cut-off value, GL = glaucoma, GON = glaucomatous optic neuropathy, HRT = Heidelberg retinal tomography, HRV = lower heart-rate variability, HTG = high-tension glaucoma, IOP = intraocular pressure, LE = left eye, MD = mean deviation score in Hodapp, NFI = nerve fiber indicator, NRA = neuroretinal rim area in HRT, NTG = normal-tension glaucoma, ONH = optic nerve head, OR = odds ratio, POAG = primary open angle glaucoma, PSD = pattern standard deviation, RE = right eye, RNFL = retinal nerve fiber layer, SD = standard deviation.

Keywords: atrial fibrillation, cardiovascular disorders, glaucoma, normal-tension glaucoma

1. Introduction

Glaucoma (GL) is a major public health problem and the second most prevalent cause of irreversible visual impairment in the western world. Primary open angle GL (POAG) is the most common type of GL, accounting for 74% of all GL cases.[1] A recent review estimated the global number of POAG cases in 2013 at 44 million, rising to 53 million by 2020 owing to population aging.[2] In white populations, the odds of POAG doubled per decade after the fourth decade. Thus, in people older than 70 years, the prevalence of POAG is approximately 8% to 10% in the white population.[3] The term "open" means that an eye has an open anterior chamber angle and "primary" refers to the fact that there are no other reasons for the optic nerve damage (e.g., ileitis, trauma, diabetic retinopathy, corticosteroid use).

POAG is characterized by a slowly progressive remodeling of the optic nerve head (ONH) and a loss of the retinal nerve fiber layer (RNFL) in combination with corresponding visual field defects. POAG has been divided into high-tension open-angle glaucoma, wherein the intraocular pressure (IOP) is elevated >21 mmHg, and normal-tension glaucoma (NTG), wherein IOP, by definition, falls within a statistically normal range and does not exceed 21 mmHg.[3,4]

Before the advanced stages, POAG may be asymptomatic, and most diagnoses occur during a routine ophthalmologic examination. Results of multicenter population-based studies have shown that lowering IOP is an effective method to slow the progression in terms of visual field survival.[4,5]

GL remains a multifactorial optic neuropathy of unknown etiology. Elevated IOP is the most important risk factor for the disease, although the exact pathways of glaucomatous optic

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neuropathy and the associated visual field loss have not yet been elucidated.[3,4].

Several potential risk factors for the development and progression of GL, in addition to IOP, have been identified.[5] Cardiovascular disorders such as systemic hypertension, hypotension, increased blood viscosity, vasospasm, and diabetes are known as potential risk factors, especially when IOP is not elevated.[6–13] In spite of known associations between cardiovascular diseases, only a few studies have reported a possible correlation between cardiac arrhythmias and GL.[14–19]

The vascular risk factors are more clearly visible in patients with NTG. According to results of the Collaborative Normal Tension Glaucoma Study, approximately 20% of NTG patients have progressive visual field deterioration despite IOP reduction.[20]

Broadway and Drance[6] found that patients with NTG had a greater prevalence of cardiovascular disease and more circulatory abnormalities in their retrobulbar vessels in comparison with other groups of glaucomatous patients. Vasospasm is a vascular risk factor for NTG, causing the reduction in blood flow and ischemic damage of RGC. Autoregulation of retinal circulation is also impaired by the vasospasm.[6] Primary vascular dysfunction has been considered as an important risk factor for the progression of GL in NTG.[21–23] Besides systemic hypertension and hypotension, patients with lower heart-rate variability (HRV) may present faster central visual field deterioration than those with greater heart-rate variability.[23] HRV is the physiological phenomenon of the variation in the time interval between heartbeats. Reduced HRV has been shown to be a predictor of high cardiovascular risk factor.

The concept that vascular changes in the eye may be an early indicator of heart diseases was also presented by Flammer et al.[24]

Like GL, atrial fibrillation (AF) is a disease of significant social importance. AF is one of the most common supraventricular arrhythmias, which is quite easy to detect. This type of arrhythmia is characterized by a completely irregular heart rate. In 2010, the estimated number of people with AF worldwide was >33 million.[25] The number of patients with AF is predicted to rise steeply in the coming years. By 2030, 14 to 17 million AF patients are anticipated in the European Union alone.[26]

AF remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity. It is independently associated with a 2-fold increased risk of all-cause mortality in women and a 1.5-fold increased risk in men.[27]

Cerebrovascular events are major complications of AF. It has been estimated that as many as 30% of all ischemic strokes are AF-related.[27] Although the relationship between AF and ischemic stroke is well documented, there is much less information regarding the effects of this type of arrhythmia on other vascular disorders. The eye is among the organs potentially threatened by the adverse effects of AF-related embolism, especially the optic nerve and retinal ganglion cells, which are particularly sensitive to ischemia. Even transient ischemia of the optic nerve can raise the risk of GL development. Such a situation can be observed among patients prone to transient hypotensive episodes (e.g., during intensive hypotensive treatment).[28–30] A similar situation may occur in AF.

The purpose of this study was to evaluate the influence of AF on morphological and functional changes in the ONH characteristic for GL in the group of elderly patients.

2. Methods

Ophthalmic examinations were conducted between October 2014 and December 2015 at the Department of Ophthalmology, Second Faculty of Medicine, Medical University of Warsaw, located in the Ophthalmic Teaching Hospital in Warsaw. The study protocol was approved by the Bioethical Commission of the Medical University of Warsaw. Each patient received both oral and written information explaining the objective and design of the study, as well as the operating principles of the devices and the course of the examination. In accordance with the Declaration of Helsinki, written informed consent was obtained from all subjects who participated in the study.

2.1. Eligibility criteria

The study group consisted of adult, white European patients with confirmed AF, according to the 2016 European Society of Cardiology guidelines for the management of AF[27] selected from the Department of Cardiology, Hypertension and Internal Diseases, Second Faculty of Medicine, Medical University of Warsaw and age-matched controls without any history of AF (also confirmed by a cardiologist consultation). All patients provided a medical history to verify inclusion and exclusion criteria.

Subjects were excluded if they had: previous history of GL; history of an acute ischemic episode of the optic nerve (anterior ischemic optic neuropathy [AION]); best corrected visual acuity (BCVA) <0.5, the presence of an exudate or a scar in the central of the retina. Eligibility for study participation was confirmed by comprehensive ocular examination. A flowchart of the study selection process is shown in Figure 1.

Participants were divided into 2 groups according to heart rhythm: that is, the control group (subjects without AF with sinus rhythm) and the AF group (patients with AF).

All patients underwent a full ophthalmic examination, including BCVA testing on Snellen chart, stereoscopic biomicroscopy of the anterior segment, IOP measurements with Goldmann applanation tonometry, gonioscopy, dilated stereoscopic fundus examination (with assessment of vertical cup to disc ratio of the ONH), Heidelberg retinal tomography (HRT; disc area, neuroretinal rim area, linear c/d ratio, mean retinal nerve fiber layer thickness; Heidelberg Engineering GmbH, Heidelberg, Germany), scanning laser polarimetry with variable corneal compensation, GDx Vcc (Laser Diagnostic Technologies, Inc., San Diego, CA) (Nerve Fiber Indicator, NFI parameter), and visual field examination on a Humphrey Field Analyzer using the Swedish Interactive Threshold Algorithm Standard 24–2 (Hodapp classification, and parameters: mean deviation score; pattern standard deviation) (Carl Zeiss Meditec, Inc., Dublin, CA).

For further analyses, only reliable results of the diagnostic tests were included: for visual field test (2 reliable tests): false-negative, false-positive, and fixation losses scores <15% for each; for GDx Vcc, Q≥8; and for HRT, standard deviation (SD) <40 μm. IOP was measured as the mean of 3 consecutive readings, with the patient in a sitting position at the slit lamp.

Diagnosis of GL was based on recommendations of the 2014 European Glaucoma Society Terminology Guidelines.[31] POAG was diagnosed if we found glaucomatous optic neuropathy (GON) and visual field defects, regardless of the IOP in one or both eyes, based on 4 criteria:

1. Morphological changes in the ONH characteristic for GON. The vertical cup to disc ratio cutoff value, c/d, to separate

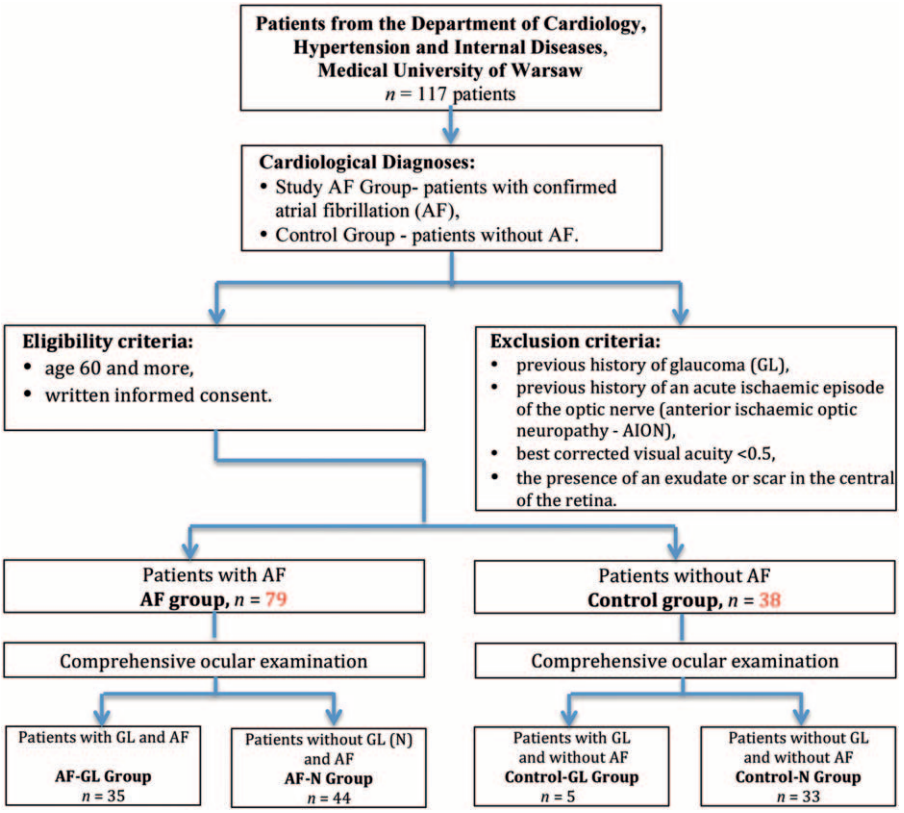

Figure 1. Flow diagram of the study selection process, AF = atrial fibrillation, GL = patients with glaucoma, N = patients without glaucoma.

GON from healthy eyes was 0.6 or asymmetry of the vertical cup to disc ratio ≥0.2 between eyes, presence of localized RNFL defects, and/or NRA defects.

2. Increased NFI value (>25) in GDx Vcc.
3. Visual field defects corresponding with RNFL thinning, in the standard automated perimetry (Humphrey Swedish interactive threshold algorithm standard 24–2 test) analyzed by the Hodapp classification.
4. Open and normal-appearing angle of the anterior chamber in gonioscopy.

High-tension glaucoma (HTN) was defined in patients with POAG and an IOP ≥22 mmHg. NTG was diagnosed when the IOP values were <21 mmHg, and there were signs of POAG.

Ophthalmic diagnostic procedures allowed for classifying the patients into 4 subgroups: AF-GL (patients with AF and diagnosed POAG [GL]); AF-N (patients with AF and without POAG [N, normal]); Control-GL (patients without AF and with diagnosed POAG); and Control-N (patients without AF and without POAG).

The sample size in each group was calculated to be >30 patients at an alpha (the type I error) of 0.05 and a power (the type II error) of 0.80 to find a reliable measurement of the NTG differentiation with the assumption of incidence in control group >0.08 and the significant incidence difference >0.30 (for uncorrected χ^2 statistic for equal number of the case and control patients).

2.2. Statistical analysis

Demographic and clinical characteristics were summarized by standard descriptive statistics (e.g., means and standard deviations for continuous variables). An independent-sample *t* test was used for normally distributed variables, and the nonparametric Mann-Whitney *U* test was used for non-normally distributed parameters. To confirm statistical significant difference between sex structures in the groups, the binominal test was used. For the case-control design in this STROBE study, we calculated the sample size in each group required to determine that NTG incidences were significantly different for the groups (e.g., >0.20) and an odds ratio (OR) is significantly different from one. The sample size and statistical power of the case–control study were calculated using Power and SampleSize Calculation software (available online: http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize) for dichotomous outcomes independent case-control samples with uncorrected χ^2 test and varying ratio of control to experimental subjects.

The ophthalmic measurements were collected from both eyes in a subset of the subjects. Kolomogorov–Smirnov and Shapiro–Wilk tests were used to determine whether the parameters were normally distributed. Because the parameters were not normally distributed, we used Wilcoxon signed rank test for comparing data from the right and the left eyes and the Mann–Whitney *U* test for comparing the AF and Control groups. All analyses were 2-tailed, and a *P* value of <.05 was considered to be significant.

3. Results

A total of 117 patients were included in the study. The AF group included 79 patients (67.5% of the study group), with 44 women and 35 men (55.7% and 44.3%, *P* = .1519). The control group included 38 patients (32.5% of the study group), with 19 women and 19 men (50% and 50%, *P* = .5625).

Baseline demographic characteristics showed no difference in terms of age, sex, and systemic vascular diseases, including

Table 1

Summary of demographic characteristics and coexisting systemic diseases of the 2 groups.

Variable	Whole group		AF group		Control group		P
	n	Mean ± SD	n (%)	Mean ± SD	n (%)	Mean ± SD	
Age, y	117 (100%)	72.9 ± 6.5	79 (67.5%)	73.6 ± 7.2	38 (32.5%)	71.4 ± 4.3	.1223*
	n	%n	n	%n	N	%n	
Females	63	53.9%	44	55.7%	19	50.0%	.5625†
		0.2328†,‡		0.1519†,‡			
CHF	37	31.6%	30	38.0%	8	21.1%	.0665†
HTN	108	92.3%	71	89.9%	37	97.4%	.1533†
DM 2	35	29.9%	26	32.9%	9	23.7%	.3088†
Stroke	8	6.8%	4	5.1%	3	7.9%	.5507†

AF = atrial fibrillation, Control = sinus rhythm, CHF = congestive heart failure, HTN = hypertension, DM 2 = diabetes mellitus type 2.

* Mann-Whitney *U* test.

† Binominal test.

‡ *P* value for females vs. males in the group.

hypertension, congestive heart failure, type 2 diabetes, and stroke between the groups.

The mean ± SD age was 73.6 ± 7.2 and 71.4 ± 4.3 years ($P = .122$) for the AF and control groups, respectively. Table 1 shows a summary of demographic characteristics and coexisting systemic diseases of the 2 groups.

Glaucoma was confirmed in 40 patients (34.2%) in the entire group. In all cases, we diagnosed NTG. There were 35 (44.3%) patients with this diagnosis in the AF group and 5 (13.15%) in the control group (Mann-Whitney *U* test, $P = .0221$ for glaucoma presence; relationship between the groups, $\chi^2 = 11.06$, $P = .00088$).

Women represented 60% (21/35) of glaucoma patients in the AF group and 80% (4/5) in the control group. The odd of glaucoma was >5 times higher in the AF group than in the control group (OR = 5.25, 95% confidence interval : 1.86–14.85, $P = .0018$).

There were no statistically significant differences in IOP values between the AF and control groups (mean ± SD, right eye [RE] 14.3 ± 2.3 vs. 14.0 ± 2.7 mmHg, $P = .4202$ and left eye [LE] 14.5 ± 2.6 vs. 14.2 ± 3.0 mmHg, $P = .5277$). Significant differences were found between the groups in the c/d ratio. The mean ± SD c/d ratio in RE was 0.466 ± 0.198 and 0.366 ± 0.148 in the AF and control groups, respectively (Mann-Whitney *U* test, $P = .0120$), and that in LE was 0.471 ± 0.193 and 0.371 ± 0.141 ($P = .0115$), respectively. Patients from the AF group had greater c/d ratio in both eyes when compared to the control group. There were no statistically significant differences in BCVA between the AF and control groups in both eyes (mean ± SD, RE 0.778 ± 0.192 vs. 0.768 ± 0.211, $P = .9397$ and LE 0.804 ± 0.202 vs. 0.784 ± 0.194, $P = .5277$). Table 2 shows results of ophthalmic diagnostic tests for glaucoma for the entire study group.

Table 2

Results of ophthalmic diagnostic tests for glaucoma for the entire study group.

Variable	Whole group (n = 117) m ± SD	AF group (n = 79) m ± SD	Control group (n = 38) m ± SD	P*
BCVA_RE	0.775 ± 0.197	0.778 ± 0.192	0.768 ± 0.211	.9397
BCVA_LE	0.797 ± 0.198	0.804 ± 0.202	0.784 ± 0.194	.5277
IOP_RE	14.2 ± 2.4	14.3 ± 2.3	14.0 ± 2.7	.4202
IOP_LE	14.4 ± 2.7	14.5 ± 2.6	14.2 ± 3.0	.5664
C/D_RE	0.433 ± 0.188	0.466 ± 0.198	0.366 ± 0.148	.0120
C/D_LE	0.438 ± 0.183	0.471 ± 0.193	0.371 ± 0.141	.0115
MD_RE	−3.22 ± 4.04	−3.56 ± 4.43	−2.52 ± 3.01	.2857
MD_LE	−2.57 ± 3.93	−3.12 ± 4.21	−1.45 ± 3.03	.1348
PSD_RE	3.36 ± 2.10	3.55 ± 2.32	2.96 ± 1.51	.2336
PSD_LE	2.97 ± 2.04	3.20 ± 2.34	2.49 ± 1.11	.1888
NFI_RE	20.84 ± 9.92	20.99 ± 11.05	20.53 ± 7.13	.9768
NFI_LE	19.90 ± 10.45	19.87 ± 12.33	19.95 ± 4.69	.4286
NRA_RE	1.54 ± 0.36	1.51 ± 0.32	1.60 ± 0.44	.9198
NRA_LE	1.56 ± 0.36	1.52 ± 0.34	1.64 ± 0.40	.2515
LIN_C/D_RE	0.446 ± 0.194	0.468 ± 0.189	0.398 ± 0.199	.0858
LIN_C/D_LE	0.444 ± 0.190	0.467 ± 0.190	0.398 ± 0.183	.0834
RNFL_RE	0.209 ± 0.077	0.200 ± 0.073	0.227 ± 0.084	.0302
RNFL_LE	0.225 ± 0.109	0.218 ± 0.120	0.241 ± 0.082	.0844
HODAPP_RE	59.8%†; 35.0%‡	50.6%†; 41.8%‡	78.9%†; 21.1%‡	.0845
HODAPP_LE	65.0%†; 29.1%‡	54.4%†;36.7%‡	88.8%†; 13.2%‡	.0846

AF = atrial fibrillation, BCVA = best corrected visual acuity, C/D = cup to disc ratio, HODAPP = visual field defect classified by HODAPP glaucoma grading scale, IOP = intraocular pressure (mmHg), LE = left eye, LIN. C/D = linear c/d in HRT, m = mean value, MD = mean deviation (dB), NFI = nerve fiber indicator in GDx Vcc, NRA = neuroretinal rim area in HRT (mm^2), PSD = pattern standard deviation (dB), RE = right eye, RNFL = retinal nerve fibre layer thickness in HRT (mm), SD = standard deviation.

* Mann-Whitney *U* test.

† Percentage of patients with stage 0 in glaucoma grading scale.

‡ Percentage of patients with stage 1 in gluacoma grading scale.

Table 3

Results of ophthalmic diagnostic tests for glaucoma in the AF group.

Variable	AF-GL group		AF-N group		P^*
	m ± SD	M ± IQR	m ± SD	M ± IQR	
BCVA_RE	0.811 ± 0.183	0.800 ± 0.300	0.752 ± 0.197	0.750 ± 0.350	.1978
BCVA_LE	0.777 ± 0.191	0.800 ± 0.300	0.825 ± 0.209	0.900 ± 0.300	.1611
IOP_RE	14 ± 2	15 ± 2	14 ± 3	14 ± 4	.6713
IOP_LE	15 ± 3	14 ± 5	14 ± 3	15 ± 4	.9921
C/D_RE	0.649 ± 0.138	0.600 ± 0.100	0.320 ± 0.085	0.300 ± 0.100	<.001
C/D_LE	0.654 ± 0.120	0.700 ± 0.100	0.325 ± 0.084	0.300 ± 0.100	<.001
MD_RE	−4.11 ± 4.10	−2.72 ± 3.21	−3.12 ± 4.68	−2.10 ± 2.66	.1397
MD_LE	−4.44 ± 5.51	−2.59 ± 3.56	−2.08 ± 2.39	−1.64 ± 1.92	.0333
PSD_RE	3.92 ± 2.99	2.76 ± 2.82	3.25 ± 1.55	2.72 ± 2.25	.9679
PSD_LE	3.85 ± 2.98	3.00 ± 2.00	2.74 ± 1.62	2.00 ± 1.00	.0945
NFI_RE	24.4 ± 12.2	25.0 ± 15.0	18.3 ± 9.3	17.5 ± 10.0	.0073
NFI_LE	23.9 ± 14.0	23.0 ± 13.0	16.7 ± 9.8	17.5 ± 12.0	.0188
NRA_RE	1.35 ± 0.30	1.39 ± 0.36	1.64 ± 0.27	1.65 ± 0.25	<.001
NRA_LE	1.41 ± 0.37	1.39 ± 0.49	1.62 ± 0.29	1.63 ± 0.40	.0032
LIN_C/D_RE	0.628 ± 0.100	0.640 ± 0.140	0.342 ± 0.140	0.376 ± 0.230	<.001
LIN_C/D_LE	0.613 ± 0.138	0.617 ± 0.184	0.350 ± 0.138	0.394 ± 0.218	<.001
RNFL_RE	0.171 ± 0.060	0.177 ± 0.077	0.224 ± 0.075	0.223 ± 0.106	.0018
RNFL_LE	0.180 ± 0.081	0.183 ± 0.112	0.248 ± 0.138	0.226 ± 0.095	.0075
HODAPP_RE	28.6%†; 57.1%‡	1 ± 1	68.2%†; 29.5%‡	0 ± 1	.0010
HODAPP_LE	34.3%†; 48.6%‡	1 ± 1	70.5%†; 27.3%‡	0 ± 1	.0037

AF = atrial fibrillation, AF-GL = patients with atrial fibrillation and diagnosed glaucoma, AF-N = patients with atrial fibrillation without glaucoma, BCVA = best corrected visual acuity, C/D = cup to disc ratio, HODAPP = visual field defect classified by HODAPP glaucoma grading scale, IOP = intraocular pressure (mmHg), LE = left eye, LIN. C/D = linear c/d in HRT, m = mean value, M = median value, MD = mean deviation (dB), NFI = nerve fiber indicator in GDx Vcc, NRA = neuroretinal rim area in HRT (mm^2), PSD = pattern standard deviation (dB), RE = right eye, RNFL = retinal nerve fibre layer thickness in HRT (mm), SD = standard deviation.

* Mann-Whitney *U* test.

† Percentage of patients with stage 0 in glaucoma grading scale.

‡ Percentage of patients with stage 1 in glaucoma grading scale.

m: mean value; M: median value; SD: standard deviation; IQR: interquartile range;

The AF group was divided into 2 subgroups: the AF-GL with NTG patients (35/79, 44.3%) and the AF-N without glaucoma. There were no differences in BCVA and IOP between these subgroups ($P = .1978$ and $P = .1611$ for RE and LE, and $P = .6713$ and $P = .9921$ for RE and LE, respectively). There were significant differences in c/d ratio in both eyes between subgroups (c/d mean ± SD, RE: 0.649 ± 0.138 vs. 0.320 ± 0.085, $P < .001$ and LE: 0.654 ± 0.120 vs. 0.325 ± 0.084, $P < .001$).

After performing diagnostic tests for glaucoma patients in the AF-GL group differed significantly from patients in the AF-N group in terms of NRA, linear c/d ratio, mean RNFL in HRT in RE and LE, NFI in GDX Vcc in RE, and visual field parameters in RE and LE. Approximately three-fourths of patients in the AF-GL group were diagnosed with early visual field damage based on the Hodapp classification. Five eyes were diagnosed with moderate and 3 eyes with advanced glaucomatous changes. Table 3 shows the results of ophthalmic diagnostic tests for glaucoma for patients in the AF group.

In the control group, NTG was diagnosed in 5 patients (5/38, 13.2%). They were included in the control-GL group. The rest of the patients from the control group without diagnosed glaucoma created the Control-N group. There were no differences in BCVA and IOP between these subgroups ($P = .9140$ and $P = .1670$ for RE and LE, and $P = .0731$ and $P = .1737$ for RE and LE, respectively). There were significant differences in c/d ratio in both eyes between subgroups (c/d mean ± SD, RE 0.620 ± 0.130 vs. 0.327 ± 0.107, $P = .0010$ and LE 0.540 ± 0.167 vs. 0.345 ± 0.120, $P = .0165$).

After performing diagnostic tests for glaucoma, significant differences between the subgroups were observed in the terms of NRA in RE, linear c/d ratio, mean RNFL in HRT in RE and LE, and visual field parameters in RE and LE. Visual fields defects found in the glaucoma patients were classified as early according to the Hodapp classification. Table 4 shows the results of ophthalmic diagnostic tests for glaucoma for patients without AF (the control group).

4. Discussion

In this study carried out within a sample of people with diagnosed AF, the common most cardiac arrhythmia, we analyzed structural changes in the ONH morphology and retinal nerve fiber and visual field defects, which allowed us to diagnose GON. We suspected that even small emboli, which are impossible to be found in the routine fundus examination, might be responsible for transient ischemic episodes in the retina and the ONH, resulting in defects arbitrary found in glaucoma. The results of our study suggest that elderly patients with AF demonstrate signs of NTG more commonly than we expected for the general population at the same age range. This percentage of glaucoma cases has been also higher than in the control group consisted of the age-matched patients with similar cardiovascular diseases.

The association between AF and retinal vessels occlusion has been documented.[32–37] In the course of AF, there are conditions favorable to the creation of intracardiac thrombus (mainly in the left atrial appendage) that may cause macro- and micro-embolism.[38] Macroembolic complications frequently manifest as transient ischemic attacks and ischemic stroke. Complications that result from microembolic events are much more difficult to diagnose. Embolism etiology is the most common reason for retinal vessel occlusion, but an embolus often may go unnoticed in clinical ophthalmologic practice.[35,36] Occlusion of posterior

Table 4

Results of ophthalmic diagnostic tests for glaucoma in the Control group.

Variables	Control-GL group		Control-N group		P^*
	m ± SD	M ± IQR	m ± SD	M ± IQR	
BCVA_RE	0.740 ± 0.270	0.800 ± 0.200	0.773 ± 0.205	0.800 ± 0.300	.9140
BCVA_LE	0.640 ± 0.251	0.700 ± 0.100	0.806 ± 0.178	0.800 ± 0.300	.1670
IOP_RE	16 ± 2	16 ± 2	14 ± 3	13 ± 3	.0731
IOP_LE	16 ± 2	15 ± 3	14 ± 3	14 ± 4	.1737
C/D_RE	0.620 ± 0.130	0.600 ± 0.200	0.327 ± 0.107	0.300 ± 0.200	.0010
C/D_LE	0.540 ± 0.167	0.500 ± 0.200	0.345 ± 0.120	0.300 ± 0.100	.0165
MD_RE	−5.91 ± 3.65	−6.62 ± 3.82	−2.00 ± 2.60	−1.32 ± 3.11	.0234
MD_LE	−0.57 ± 7.00	−2.86 ± 4.42	−1.58 ± 2.08	−1.51 ± 2.86	.6975
PSD_RE	4.79 ± 2.46	5.14 ± 4.03	2.68 ± 1.13	2.35 ± 1.48	.0841
PSD_LE	3.60 ± 1.52	3.00 ± 1.00	2.39 ± 0.97	2.00 ± 1.00	.0633
NFI_RE	21.6 ± 4.8	22.0 ± 3.0	20.4 ± 7.5	20.0 ± 8.0	.7460
NFI_LE	21.0 ± 5.9	24.0 ± 7.0	19.8 ± 4.6	20.0 ± 5.0	.5171
NRA_RE	1.19 ± 0.18	1.12 ± 0.17	1.66 ± 0.44	1.53 ± 0.57	.0072
NRA_LE	1.44 ± 0.19	1.42 ± 0.37	1.67 ± 0.41	1.61 ± 0.66	.2615
LIN_C/D_RE	0.677 ± 0.040	0.676 ± 0.019	0.355 ± 0.177	0.382 ± 0.221	.0006
LIN_C/D_LE	0.585 ± 0.122	0.517 ± 0.223	0.370 ± 0.175	0.382 ± 0.272	.0156
RNFL_RE	0.103 ± 0.043	0.089 ± 0.010	0.246 ± 0.071	0.268 ± 0.092	.0017
RNFL_LE	0.170 ± 0.048	0.148 ± 0.045	0.252 ± 0.081	0.257 ± 0.114	.0175
HODAPP_RE	20.0%†; 80.0%†	1 ± 0	87.9%†; 12.1%‡	0 ± 0	.0165
HODAPP_LE	20.0%†; 80.0%†	1 ± 0	97.0%†; 3.0%‡	0 ± 0	.0065

BCVA = best corrected visual acuity, Control-GL = patients without atrial fibrillation and with diagnosed glaucoma, Control-N = patients with atrial fibrillation without glaucoma, C/D = cup to disc ratio, HODAPP = visual field defect classified by HODAPP glaucoma grading scale, IOP = intraocular pressure (mmHg), LE = left eye, LIN. C/D = linear c/d in HRT, m = mean value, M = median value, MD = mean deviation (dB), NFI = nerve fiber indicator in GDx Vcc, NRA = neuroretinal rim area in HRT (mm^2), PSD = pattern standard deviation (dB), RE = right eye, RNFL = retinal nerve fibre layer thickness in HRT (mm), SD = standard deviation.

* Mann–Whitney *U* test.

† Percentage of patients with stage 0 in glaucoma grading scale.

‡ Percentage of patients with stage 1 in glaucoma grading scale.

cilliary vessels may cause sudden ischemia of the optic nerve and development of AION. In this case, sudden visual acuity impairment occurs with typical changes in the fundus, including optic disc edema, and hemorrhages. AION may result in the optic nerve damage, with an increased c/d ratio. These changes can resemble GON. Typically in the course of glaucoma, there is no sudden visual impairment, but transient ischemic episodes may lead to perfusion disorders and death of RGCs. Microembolisms released from the heart in the course of AF may be a possible mechanism behind this. These changes can remain unnoticed for a long time because they do not cause any sudden changes in visual quality.

A previous thromboembolic event in the retina should be also considered as a strong risk factor for a similar cerebrovascular event in the future in patients with AF.[33] The results of the EAGLE Group study showed that previously undiagnosed vascular risk factors, mainly carotid artery stenosis (40%), were found in 78% of all patients with nonarteritic central retinal artery occlusion.[28] Coronary artery disease, AF, and valvular heart disease were also highly prevalent, accounting 22%, 20%, and 17%, respectively.[34]

Güngör et al[39] found that patients with a history of ischemic cerebrovascular incidents had also a higher incidence of NTG, probably because of the similar origin of the disorders, namely small arterioles occlusion.

Several studies reported a higher incidence of AF in patients with POAG, and especially in NTG.[14,16–18] In elderly adults, Peräsalo et al found that the percentage of AF was significantly higher in patients with POAG then in healthy subjects (17% vs. 8%).[17,18] Patients with AF also presented lower visual acuity, and severe visual field defects occurred more frequently in this group (70% vs. 42%).[17] Analyzing these results in addition to ours, we also found more frequently visual field changes, even moderate to advanced, at the time of NTG diagnosis, in patients with AF than in the Control group.

Both AF and NTG are highly dependent on age: the older the patient, the greater the risk of glaucoma and/or AF development. Similar to the study of Peräsalo et al, we performed examinations in patients older than 60 years of age. It is estimated that at this age range, POAG occurs in up to 8% to 10% of people. We matched patients with the same age and the same cardiovascular disorders, so the only difference was the status of the heart rhythm.

As expected, glaucoma was diagnosed in the control group in slightly higher percentage than in general population, what may be associated with the presence of the vascular risk factors. NTG was diagnosed almost 3 times more often in patients with AF than in the control group.

The relationship between glaucoma and blood pressure remains under debate. Data from many studies provide support for systemic hypertension as an important factor in POAG incidence and progression.[4,7,10,12,19,24,40,41] Although some other studies indicate that low systemic blood pressure is a risk factor for the development and progression of glaucoma. A direct and clear relationship between glaucomatous damage and blood pressure level has not been established.[42] In our study, the incidence of hypertension was high and similar in the AF and control groups.

AF is quite easy to detect by finding completely irregular heart rate in the ECG. Importantly, a substantial proportion of patients with AF, similarly as in glaucoma, is asymptomatic or oligo-symptomatic. The early diagnosis of glaucoma is not so simple especially when the IOP is in normal range and the patient has no eye complaints. The early diagnosis of glaucoma might help prevent later visual impairment and even irreversible blindness.

Based on the results of our study, we suggest that the presence of AF, regardless other known cardiovascular risk factors, may be a strong risk factor for NTG in elderly patients because of high odds in the AF group. Population-based multicentric studies are necessary for a strict judgement. Physicians should pay close attention to patients with the chronic cardiovascular comorbidities and AF among them and if found refer the patient to an ophthalmologist for NTG screening to prevent loss of vision. Therefore, we recommend screening for glaucoma in patients with diagnosed AF.

4.1. Study limitations

The present study has some specific characteristics and limitations that should be addressed. First, we defined IOP within the normal range without considering diurnal IOP variation and central corneal thickness influence on applanation tonometry measurements. Second, there is a need for further follow-up because it is possible that some eyes will develop glaucoma over time. Finally, the association analysis based on AF and glaucoma was conducted in a relatively small sample size. Especially, the control group seemed to be relatively small because of restricted exclusion criteria; however, sufficient statistical power (>.80 and the post-hoc tested power for the conducted study was equal to .948) to detect the NTG incidence effect is relatively high.

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