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Identification of comorbid pathology in patients with atrial fibrillation

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The aim of the study is to determine the incidence of comorbid diseases in associated with atrial fibrillation (AF).

Methods. The one-phase study included 134 patients (72 men and 62 women) with a confirmed diagnosis of atrial fibrillation. Patients underwent anthropometric examination (height, weight, body mass index), blood pressure (BP) measurement, resting electrocardiography, Doppler echocardiography, ultrasonography. Thyroid hormonal status (free T3, free T4, thyroid stimulating hormone, anti-TG, and antibodies to thyroperoxidase) was also examined. Thyroid hormones were analyzed by enzyme-linked immunosorbent assay using Bio Screen MS-500 (USA).

Results. The distribution of atrial fibrillation by form was as follows: paroxysmal form was registered in 26 (19.4%) patients, persistent — in 7 (5.2%), long-term persistent — in 19 (14.2%), and permanent — in 79 (59.0%). Arterial hypertension (AH) was detected in 81 patients (60.4%) with AF, chronic heart failure (CHF) in 82.8%, type 2 diabetes mellitus in 26 (19.4%), and coronary heart disease (CHD) in 42 (31.3%). Ischemic stroke was registered in 9 (6.7%) patients with a history of AF.

One somatic comorbidity was found in 25 (18.8%) patients, two in 40 (29.3%), three in 44 (32.8%), four in 19 (14.5%), and five in 6 (4.6%).

Approximately 80% of patients with AF were at high risk for stroke and thromboembolic complications without anticoagulant therapy.

Conclusion. The majority of AF patients are diagnosed with other cardiovascular diseases, including AH, CHD and CHF. In the surveyed group, a combination of two and three diseases was detected in more than 60% of cases.

Keywords: atrial fibrillation, comorbidity, somatic diseases.

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Introduction

Atrial fibrillation (AF) is the most common type of supraventricular arrhythmia, causing serious hemodynamic disturbances and complications. Despite some progress in the treatment of AF, this type of arrhythmia remains one of the leading causes of stroke, chronic heart failure (CHF) and sudden cardiac death. In addition, the incidence of this condition is expected to increase in the coming years [1].

The prevalence of AF worldwide is 3 % in the population over 20 years of age [2, 3]. In Europe and the USA, one in four middle-aged people is at high risk of developing AF. It should be noted that the prevalence of AF in the elderly is increasing, including in the presence of comorbidities — arterial hypertension (AH), coronary heart disease (CHD), heart failure (HF), obesity, diabetes mellitus (DM), thyroid pathology, chronic kidney disease (CKD) [1-4].

AF has both a symptomatic and asymptomatic course. Latent asymptomatic AF can lead to serious complications such as stroke and death [5]. Population screening with resting ECG to detect asymptomatic AF, especially in the elderly and those with AF-related diseases, is recommended [5].

Prevention, early detection and appropriate correction of risk factors leading to AF and other comorbidities play an important role in the management of AF and its complications [6, 7]. The most common comorbidities include CHD, CHF, AH, cardiomyopathies, chronic obstructive pulmonary disease, thyroid pathology, DM and others. In most cases, the average number of comorbidities in patients with AF is 3–4 [1]. These diseases can act both as the primary cause of AF and as comorbidities, and thus pathogenetically contribute to the progression of AF, reduce the quality of life of patients, and increase the risk of complications and sudden cardiac death [8, 9].

The aim of the study was to determine the incidence of comorbid conditions associated with AF of non-valvular genesis.

Methods

The one-phase cohort clinical study included 134 patients (72 males and 62 females) aged 18 years and older (mean age 62.8 years; 95 % confidence interval (CI) — 60.9; 64.6) with various forms of AF who were being followed as inpatients and outpatients at the Mirgasimov Republican Clinical Hospital. The presence of atrial fibrillation was documented according to the data of 12-lead electrocardiographic (ECG) series, including during ECG Holter monitoring. According to AF classification, 29 patients (21.6 %) of 134 patients were diagnosed with paroxysmal AF, 7 patients (5.2 %) with persistent AF, 19 patients (14.2 %) with long-term persistent AF, and 79 patients (59.0 %) with permanent AF, including 16 patients (11.9 %) with first-time AF.

All patients were divided into 3 groups according to the ECG variant of AF: Group 1–29 patients with paroxysmal AF, Group 2–26 patients with persistent and long-term persistent AF, and Group 3–79 patients with permanent AF. Complex clinical. instrumental and laboratory investigations revealed the presence of various comorbid diseases and clinical conditions (Table 1). AH was found to be the most common pathology associated with AF among the patients studied. Among 81 patients with AH (60.4 %; 95 % CI — 52.14, 68.76), stage I (uncomplicated) was found in 22 patients, stage II (asymptomatic) in 36 patients, and stage III (complicated) in 23 patients.

Table 1

Clinical characteristics of the examined patients

Criteria	Group 1 (n=29)	Group 2 (n=26)	Group 3 (n=79)
Males/females, n	20 / 9	16 / 10	42 / 37
Age, years	50.3 (48.4; 56.3)	56.6 (52.8; 60.3)	65.8 (56.1; 68.2)
History of myocardial infarction, n / %	2 / 6.9	3 / 11.5	11 / 13.9
History of stroke, n / %	—	2 / 7.7	7 / 8.9
Type 2 DM, n / %	4 / 13.8	5 / 19.2	17 / 21.5
AH, n / %	16 / 55.2	17 / 65.4	48 / 60.8
CHF, functional classes II–IV, n / %	12 / 41.4	20 /76.9	79 /100.0
Anemia (Hb <110 g/l), n / %	2 / 6.9	2 / 7.7	13 / 13.9
Obesity, classes 1–3, n / %	6 / 20.7	5/ 19.2	12 / 15.2
Left ventricle hypertrophy, n / %	11 / 37.9	13 / 50.0	40 / 50.6
CKD, stages 2-3	13 / 17.3	8 / 17.0	21 / 17.2

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Exclusion criteria were: congenital and/or acquired valvular heart disease; isolated atrial fibrillation; patients who underwent catheter radiofrequency ablation of the pulmonary vein orifices; clinically and laboratory confirmed hypo- and hyperthyroidism; use of drugs affecting thyroid function; refusal to participate in the study.

Patients underwent the following examinations: clinical examination, anthropometric measurements (height and weight were measured, body mass index was calculated), blood pressure (BP) measurement, resting ECG in 12 standard leads, Doppler echocardiography, ultrasound examination of the thyroid gland and internal organs. Doppler echocardiographic data were used to calculate structural and functional parameters of the heart: heart chambers dimensions, wall thickness, global systolic function, left ventricle myocardial mass index (LVMI). In case of sinus rhythm, i.e. in paroxysmal and persistent atrial fibrillation, LV diastolic function was assessed.

The European Heart Rhythm Association (EHRA) scale was used to assess the clinical severity of atrial fibrillation. Thyroid hormonal status was assessed (free T3, free T4, TSH, anti-TG and antibodies to thyroperoxidase). The analysis of thyroid hormones was performed by enzyme immunoassay on the Bio Screen MS-500 device (USA) with the reagent of Chema LLC (Moscow).

To assess the comorbidity of somatic diseases, the verified diseases registered in medical documents were taken into account. AH was confirmed in the presence of BP ⩾140/90 mmHg in two consecutive clinical visits and in patients receiving adequate doses of antihypertensive drugs, according to the recommendations of the European Society of Cardiology/European Society of Hypertension 2018 (ESC/ESH-2018) [10]. The diagnosis of type 2 DM was verified according to the criteria of the American Diabetes Association [11]. CHF, its phenotypes and functional classes were determined on the basis of clinical and instrumental parameters (symptoms, LV ejection fraction parameters) according to the recommendations of the European Society of Cardiology [12].

The CHA_2DS_2-VASc score was calculated to decide on the prescription of anticoagulant therapy for each patient [1].

Statistical analysis

Statistical analysis was performed using standard Microsoft Excel software. During the statistical analysis of the material, the minimum, maximum and mean values of the sample, the standard deviation and the error of the mean were determined. The normality of the distribution of the variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The Student's t-test was calculated. The 95% CI of fractions was calculated using an online calculator according to the Wilson method. The CI of means for 95% probability was also determined. Calculations were performed using the Confidence Limits for Mean Calculator. For small samples, the significance of differences was determined using the Mann-Whitney U-test.

Reliability of differences between proportions was calculated using Pearson's chi-squared test (χ^2) and Fisher's exact test. Calculations for these methods were performed online using the MEDCALC calculator. Differences were considered statistically significant at $p<0.05$.

Results

Of 134 patients with AF, 28 patients were in class I, 32 patients were in class IIa, 56 patients were in class IIb, and 18 patients were in class III according to the EHRA scale. When evaluating the frequency of comorbid diseases associated with AF, it was shown that in 19.4% of cases (95% CI 73.88; 87.32) there was type 2 DM, in 23 patients — 17.2% (95% CI 10.76; 23.57) — abdominal obesity of varying severity. In 42 patients — 31.3% (95% CI 23.46; 39.23) — various clinical forms of CHD were diagnosed, including 16 patients (11.9%) with a history of myocardial infarction. In addition, 111 patients — 82.8% (95% CI 73.88; 87.32) were diagnosed with CHF, including 29 patients — 21.6% (95% CI 18.45; 35.25) of II FC, 59 patients — 44% (95% CI 45.20; 64.06) of III FC, and 23 patients — 17.2% (95% CI 11.16; 25.88) of IV FC.

When assessing the predictive role of different clinical conditions associated with AF, some peculiarities were revealed. There was a difference in the severity (stage) of CHF depending on the ECG variant of AF. In patients with permanent AF (group 3), cases of congestive CHF were predominant, whereas in patients with paroxysmal and/or persistent AF (groups 1 and 2), cases of early CHF were predominant: 83.5% vs. 50% (χ^2=13.28; p=0.0003). However, in patients with uncomplicated stages of AH, paroxysmal and/or persistent AF was significantly more common than permanent AF: 76.4% vs. 49.4% (χ^2=13.28; p=0.0017).

This implies that the presence of AH without associated clinical conditions is a risk factor for paroxysmal and/or persistent AF, whereas CHF, especially stages III–IV, is usually correlated with persistent AF.

It was also revealed that the incidence of CKD did not differ significantly between groups, although it was more frequent in group 3. However, a comparative evaluation of the estimated value of the glomerular filtration rate determined by the CKD-EPI formula revealed a significant difference between the 1-2nd and the 3rd groups. As it is known, the detection rate of cardiovascular diseases, including atrial fibrillation, increases with the age of the population. Therefore, the mean age in the group of patients with paroxysmal AF was significantly lower than in the group of patients with permanent AF: 50.3 (48.4; 56.3) and 65.8 (56.1; 68.2) years, respectively (p <0.001).

It should be noted that when comparing the functional status of patients with AF, i.e. taking into account the AF severity class according to EHRA, similar trends were obtained both depending on the ECG variant of AF. Analysis of the obtained data revealed the presence of at least one comorbid pathology in all patients with AF (table 2). Thus, 25 (18.8%) patients had one, 40 (29.3%) — two, 44 (32.8%) — three, 19 (14.5%) — four and 6 patients (4.6%) — five comorbidities. In addition, it was shown that the age of patients with 4–5 comorbidities was significantly higher than the age of patients with 1–2 comorbidities (p<0.05).

In the group of patients with 1–2 comorbidities, AH was detected significantly more often than in patients with 4 (χ^2=8.05; p=0.005) and 5 comorbidities (χ^2=3.90; p=0.048). This indicates that AH is the most common comorbid condition, especially in relatively young patients with paroxysmal AF, and is a predictor of arrhythmia development. The main markers of atrial electrical vulnerability ("arrhythmogenic readiness") are considered to be hypertensive cardiac remodeling, manifested by LV diastolic dysfunction and increased left atrial volume, P-wave dispersion and shortened refractory period [9].

In the group of patients with 5 comorbidities, CHF, especially FC III–IV, was found in all 6 patients (100.0%), also characterized by the predominance of the permanent form of AF. On the contrary, the frequency of CHF was significantly lower in patients with 1–2 comorbidities. This may be explained by the fact that in patients with permanent AF, the development of CHF with signs of fluid retention in the body is more likely to be a manifestation of tachysystolic dilated cardiomyopathy caused by AF.

To determine the risk of stroke and thromboembolic complications in patients with AF before prescribing anticoagulant therapy, the CHA2DS2-VASc score was calculated, according to which the patients were divided into 3 groups: low-risk patients — 14.5%, intermediate-risk patients — 11.6%, and high-risk patients — 73.9% (table 3).

Table 2

The prevalence of comorbid pathology combinations in patients with AF (n / %)

Parameters	Number of comorbidities			
	1–2 (n = 65)	3 (n = 44)	4 (n = 19)	5 (n = 6)
Age, years	51.3 (46.2; 50.7)	55.9 (53.8; 60.5)	63.1 (54.0; 67.8)	65.8 (58.7; 68.4)
Stage 1–3 AH, (n = 81)	47 (72.3)	25 (56.8)	7 (36.8)	2 (33.3)
CHD, (n = 41)	8 (12.3)	16 (36.4)	12 (63.2)	6 (100.0)
Type 2 DM, (n = 26)	10 (15.4)	8 (18.2)	6 (31.5)	2 (33.3)
Obesity, classes 1–3, (n = 23)	12 (18.5)	7 (15.9)	3 (15.8)	1 (16.7)
CHF, stages II–IV, (n = 111)	52 (80.0)	35 (79.6)	18 (94.7)	6 (100.0)
Paroxysmal AF, (n = 29)	15 (23.1)	10 (22.7)	3 (15.8)	1 (16.7)
Persistent AF, (n = 26)	9 (13.9)	9 (20.5)	5 (26.3)	3 (50.0)
Permanent AF, (n = 79)	30 (46.2)	27 (61.4)	16 (84.2)	6 (100.0)

Table 3

Risk of stroke and thromboembolism, history of stroke, and anticoagulant therapy in patients with AF

CHA2DS2VASc			History of stroke	Anticoagulant therapy	
Low risk	Intermediate risk	High risk	9 (6.7%)	Recieved	Did not recieve
19 (14.5%)	15 (11.6%)	100 (73.9%)		32 (23.9%)	102 (76.1%)

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It should be noted that 9 patients (6.7%) had a history of ischemic stroke. Anticoagulant therapy was used in 32 (23.9%) patients and not used in 102 (76.1%) patients. Overall, 22.4% of patients were treated with warfarin and only 1.5% with rivaroxaban.

Discussion

The single-stage study is dedicated to the investigation of somatic comorbidity in patients with different forms of AF. The relevance of this problem is due to the high risk of hemodynamic disorders and thromboembolic complications in AF [13, 14]. The most serious of these is ischemic stroke. In 20–30% of patients with a history of ischemic stroke, atrial fibrillation is found in the acute phase of the disease or after hospitalization [15-16]. In addition, vascular dementia and impaired quality of life due to cognitive impairment are common in patients with AF [17–18]. Stroke in AF is more likely to be disabling and fatal compared to other causes. Anticoagulant therapy is prescribed to reduce the risk of stroke/thromboembolism. The CHA_2DS_2VASc scale is widely used to choose therapy. If the CHA_2DS_2VASc score is > 1 in men and > 2 in women, the likelihood of thromboembolic complications increases, indicating the use of oral anticoagulants.

In our study, oral anticoagulant therapy was indicated for almost all patients, but in real clinical practice, in most cases, they were not prescribed or, when prescribed, patient compliance was low. In particular, 30 patients were prescribed warfarin as anticoagulant therapy, but the international normalized ratio recommended for its efficacy and safety was not always determined. New oral anticoagulants, which are safer than warfarin and do not require regular laboratory testing, were prescribed in only 1.5% of cases.

In patients with AH, the presence of AF significantly increases the risk of stroke and also increases the risk of CHF. At the same time, high blood pressure can increase the likelihood of stroke and hemorrhagic complications and lead to arrhythmia recurrence [19].

CHF is known to be one of the most common comorbidities in patients with AF. The development of AF in patients with CHF is associated with the presence of common pathophysiological mechanisms (structural remodeling, activation of neurohormonal mechanisms) and risk factors [20, 21]. The most severe hemodynamic disorder is tachycardia-induced cardiomyopathy, which is characterized by an unfavorable prognosis. On the other hand, patients with AF and CHF comorbidity have been shown to have a worse prognosis and increased risk of cardiovascular mortality, regardless of LV ejection fraction [22].

The presence of common risk factors of type 2 DM and AF also increases the frequency of their comorbidity. In recent years, type 2 DM has been recognized as a potential risk factor for the development of AF, which has been confirmed by numerous studies. For example, patients with diabetes were found to have a 39% higher risk of developing AF compared to those without diabetes [23]. Control of glycemic status is also important, with inadequate control increasing the risk of AF [24, 25].

In the present study, one in three patients had a combination of two or three somatic diseases. The most common combination was AF with AH and CHF. At present, one in six patients with AF has a combination of AH, CHD and CHF. Therefore, it can be assumed that AF is detected at all stages of the cardiovascular continuum, which increases the risk of complications.

Conclusion

The majority of AF patients have comorbid cardiovascular diseases, including AH, CHD and CHF. In the cohort studied, a combination of two and three diseases was found in more than 60% of cases. Approximately 80% of AF patients were at high risk for stroke and thromboembolic complications without anticoagulant therapy.

Early detection of comorbidities and complex therapy, including anticoagulant therapy, may reduce the risk of AF or its progression or the development of complications, thereby improving the quality of life and prognosis of patients with AF.

Conflict of interests: none declared.

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