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LEFT ATRIAL APPENDAGE THROMBOSIS AND FREDERICK'S SYNDROME: A CASE REPORT

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The article presents a clinical case of a young patient living in the Far North for a long time with Frederick's syndrome and diagnosed of the left atrial appendage thrombosis.

Keywords: Frederick syndrome; atrial fibrillation; complete heart block; left atrial appendage thrombus; His pacing

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Frederick's syndrome is a combination of complete atrioventricular (AV) block and atrial fibrillation (AF) or flutter, which is manifested by a complete interruption of the excitation impulses from the atria to the ventricles. In this case, the ventricles are excited by a rhythm driver from the AV junction or the ventricular conduction system, and there is a disordered contraction of individual groups of muscle fibres in the atria [1]. Frederick's syndrome occurs in 0.6-1.5% of patients with AF [1, 2]. On transoesophageal echocardiography (TOE) prior to catheter ablation or cardioversion in AF, the incidence of thrombus in the left atrial appendage (LAA) is 5.1-27.1%, depending on oral anticoagulants, and the risk of thrombus formation remains even with adequate anticoagulant therapy [3]. The aim of this paper is to present the clinical case of a young patient with Frederick's syndrome and proven LAA thrombosis according to the TOE data in the conditions of the far north over a long period of time.

Patient R., 34 years old, was admitted to the Tyumen Cardiology Research Centre in January 2020 complaining of excruciating left chest pain unrelated to physical activity, unstable blood pressure (BP), shortness of breath when ascending to the 4th floor. Past medical history: 13 years of living in the Far North (in Yamalo-Nenets Autonomous District). Medical history: In 2000 and 2012, the patient suffered severe electrical trauma with loss of consciousness on two occasions. Arterial hypertension in the last 7 years with maximum BP increase to 215/110 mm Hg, against a background of constant hypotensive therapy BP values were recorded mainly at the level of 130/90 mm Hg. Every year (1-2 times per year) he had cases of acute respiratory viral infections with an increase in body temperature up to 39-40 °C, he was treated independently as an outpatient. In 2014, after a severe viral infection, the patient noticed «interruptions» in the work of the heart for the first time; he did not seek medical help at that time. Since 2015, a series of electrocardiograms (ECG) as part of screening examinations have constantly registered a rhythm of AF with scarring changes in the left ventricle (LV); no attempts have been made to restore sinus rhythm at the residence. For the last 2 years before the present hospitalisation, the patient had a steady, infrequent pulse of 40 per minute, without clinical manifestations. At the end of December 2019, against a background of psycho-emotional stress, the complaints of excruciating

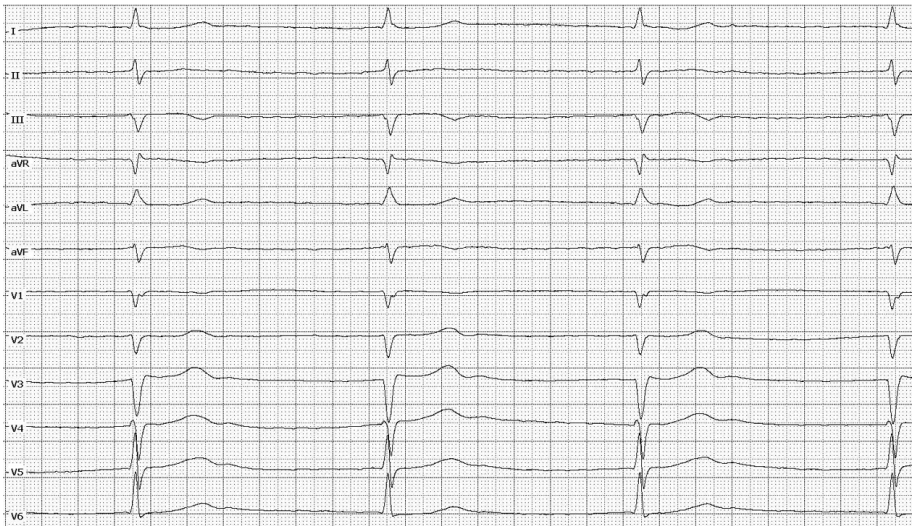

Fig. 1. Patient's ECG on admission (recording rate 50 mm/s, amplitude 10 mm/mV).

pain in the left side of the chest and general weakness appeared. With the diagnosis: coronary heart disease (CHD), unstable angina pectoris, unspecified postinfarction cardiosclerosis, the patient was admitted to the hospital at his place of residence. On admission, ECG and daily ECG monitoring revealed signs of Frederik's syndrome with a ventricular rate of 33-46-77 during the day and 28-35-62 per minute at night. Transthoracic echocardiography (EchoCG) revealed signs of dilatation of the left atrium (LA), right ventricles against a background of satisfactory contractile function of the myocardium LV. The patient underwent coronary angiography which showed a muscular bridge in the middle third of the anterior descending artery which narrowed the arterial lumen by up to 40% in systole. Against the background of medical therapy at the place of residence (losartan 50 mg/day, torasemide 2.5 mg/day, spironolactone 25 mg/day, clopidogrel 75 mg/day, dabigatran 110 mg twice daily, atorvastatin 40 mg/day), the signs of Frederick's syndrome persisted. The patient was transferred to the Tyumen Cardiology Centre for surgical intervention - permanent pacemaker implantation (PM) - via the Centre for Disaster Medicine.

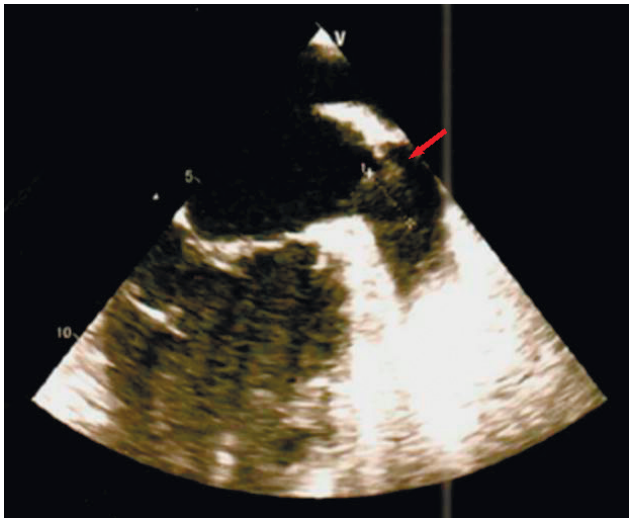

Fig. 2. TOE: soft globular parietal thrombus in LAA (arrow indicates thrombus).

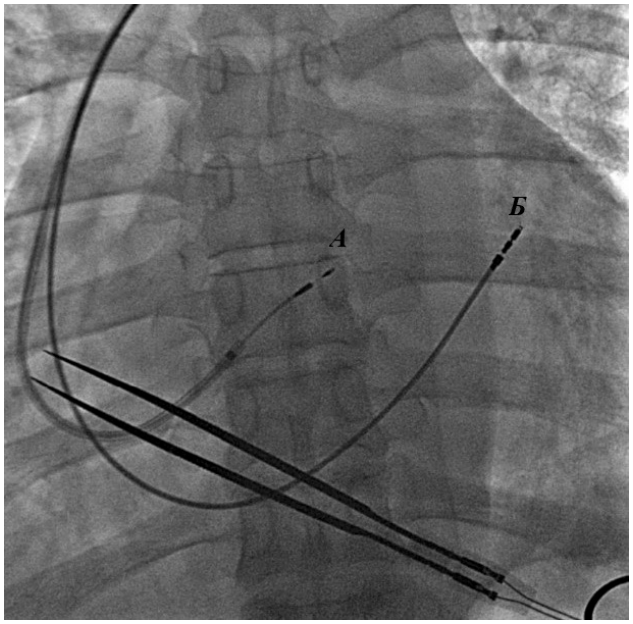

Fig. 3. Location of electrodes in the bundle branch (A) and RV septum (B) in direct projection.

At the time of admission to our centre, the ECG showed Frederick's syndrome with a ventricular contraction rate of 43 per minute combined with blockage of the anterior branch of the left bundle branch, signs of LV scar changes with anterior apical localisation, and signs of right ventricular (RV) strain were observed (Fig. 1).

According to the results of diurnal ECG monitoring, the rhythm of AF (signs of Frederick's syndrome) was constantly observed during the day, the frequency for ventricles during the day varied at the level of 31-43-70 per minute. EchoCG findings: cardiac cavity dilatation, predominantly right sections (LA - volume index 71.1 ml/m^2; right atrium (RA) - volume index 108.8 ml/m^2; RV - diameter index 20.1 mm/m^2, LV end-diastolic volume index 79.4 ml/m^2, LV end-systolic volume index 34 ml/m^2), signs of LV remodelling in the form of eccentric LV hypertrophy (LV myocardial mass index 119.8 g/m^2, relative thickness of LV wall 0.4), moderate mitral regurgitation, moderate tricuspid regurgitation, echo signs of moderate pulmonary hypertension (systolic pulmonary artery pressure 56 mm Hg), preserved LV ejection fraction (55%).The study was based on the results of the study of the patients with a small number of patients. The TOE findings showed a soft spherical parietal thrombus up to 1.5 cm in diameter in LAA, and there was moderate spontaneous echoconstriction with reduced velocity of blood flow in LAA up to 38 cm/s (Fig. 2).

Among hematological parameters, there was an increase in NT-proBNP level up to 815 pg/ml. Against the background of therapy with dabigatran in standard coagulation tests there was a 1.5-fold increase in activated partial thromboplastin time (up to 45.4 s) and 5.5-fold increase in thrombin time (up to 110 s). Other coagulogram parameters, such as D-dimer, prothrombin index, and antithrombin III, were within normal limits. Laboratory data confirmed euthyroidism (thyroid hormone - 1.01 IU/ml, free T4 - 17.8 pmol/l).

Taking into account the clinical and anamnestic data (absence of clinical symptoms typical of CHD, coronarography findings, absence of asynergia and hypokinesia zones on EchoCG), the diagnosis of CHD, previous myocardial infarctions, the final diagnosis was made: principal diagnosis: Arterial Hypertension stage III. Controlled arterial hypertension. Risk of cardiovascular complications 4 (very high). Target BP ≤130/70-79 mmHg. Complications: Rhythm and conduction disorder: Permanent AF, combined with total AV block (Frederick's syndrome). CHA_2DS_2-VASc - 2, HAS-BLED - 0. Secondary dilatation of heart cavities. Moderate pulmonary hypertension. Thrombus in LAA. Chronic heart failure IIA with preserved ejection fraction, NYHA functional class II.

The patient underwent correction of antithrombotic therapy, clopidogrel was cancelled. In view of the deviations in the coagulation indices responding to the effect of dabigatran, treatment with the thrombin inhibitor dabigatran was continued and the dose was increased to the standard dose - 150 mg twice daily.

Taking into account the absolute indications (permanent AV blockade), the patient was implanted with a

Medtronic Adapta DR dual-chamber PM with two endocardial leads: one lead was placed in the region of the bundle branch and connected to the atrial channel of the PM, the second lead was placed in the region of the RV septum to enable safety cardiac pacing and connected to the ventricular channel (Fig. 3, 4).

When programming the PM, the following parameters were determined and set: AAIR mode, lower rate limit - 60 per minute, at the parahysial electrode: stimulation threshold 1.25 V at pulse duration 0.5 ms, amplitude 4.0 V, impedance 549 ohms; at the RV electrode: stimulation threshold 1.25 V at pulse duration 0.4 ms, amplitude 3.5 V, impedance 575 ohms. During ECG recording against a background of hypotensive stimulation, an PM rhythm was recorded with a ventricular rate of 60 ppm, and the width of the QRS complex was 100 ms and did not differ from the QRS complex in spontaneous rhythm (Fig. 4b).

One week after surgery, a repeat EchoCG was performed, which showed a positive trend in the form of a decrease in the size of LA (volume index from 71.1 to 55.7 ml/m^2), the right heart (the volume index of RA from 108.8 to 82, 5 ml/m^2, RV diameter index from 20.1 to 19.1 mm/m^2), decrease in mitral regurgitation to mild and tricuspid regurgitation to moderate, systolic pressure in the pulmonary artery (from 56 to 38 mm Hg), increase in ejection fraction to 57%.

At discharge, the patient was advised to continue the drug therapy chosen in hospital (losartan 50 mg/day, spironolactone 25 mg/day, dabigatran 150 mg twice daily), atorvastatin was discontinued because the diagnosis of CHD was excluded.

After 3 months, the patient was repeatedly hospitalized to our center for dynamic examination and optimization of PM parameters. At admission, the patient had no active complaints. The ECG and daily ECG monitoring recorded an PM rhythm with a frequency of 62 per minute; against a background of physical activity, the rhythm increased up to 98 per minute. EchoCG data showed continued positive dynamics in the form of a further decrease in LA volume index to 49 ml/m^2, RA to 77.3 ml/m^2, mitral and tricuspid regurgitation to grade 1, systolic pulmonary artery pressure to 36 mm Hg, LV myocardial mass index to 106.7 g/m^2. The patient underwent a repeat TOE against a background of continuous dabigatran dosing of 300 mg/day: there was no evidence of thrombosis and spontaneous echocontrast in LAA, there was an increase in velocity indices up to 56 cm/s (Fig. 5). Among hematological parameters, the normalization of NT-proBNP index (101 pg/ml) was noted in the dynamics. When programming the PM parameters, the stimulation threshold at the electrode in the bundle branch area was 1.5 V, and the pulse amplitude was reduced to 3.25 V. The repeated study of the patient one year after PM implantation (ECG, EchoCG, TOE, examination of the PM system, NT-pro BNP index) did not reveal any negative dynamics. During the year, the patient continued to take the prescribed drug therapy in the former doses (losartan, spironolactone, dabigatran). Repeated TOE showed no signs of thrombus in LAA.

DISCUSSION

This clinical case is of interest from several points of view.

Firstly, this case shows a long asymptomatic course in a patient with complete AV block on a background of permanent AF (Frederick's syndrome), which developed due to an unspecified cause and led to the development of arrhythmogenic cardiomyopathy.

In our clinical example, the absence of clinical manifestations of arrhythmia against the background of the subjective sensation of a rhythmic pulse may have led to the incorrect assessment that the patient had sinus rhythm and that timely recognition of Frederick's syndrome was not possible. In addition, the narrow QRS complexes (up to 100 ms) in this patient's ECG indicate the localisation of the rhythm driver in the AV junction and speak for a proximal type of block, which is often not accompanied by a disturbance of the biomechanical cardiac contraction [4]. In the Russian literature, a case was described in which bradycardia was not diagnosed in time against a background of permanent atrial fibrillation (Frederick's syndrome), which led to syncope in one patient and delayed the implantation of an PM [2].

One of the possible causes of concomitant rhythm and conduction disturbances in this patient may be myocarditis. This version can be supported by the history of cardiac arrhythmias associated with repeated viral infections as well as the involvement of all cardiac chambers in the pathological process, while due to the age of the disease we have no confirmation by laboratory and instrumental examination methods of the diagnosis of myocarditis. Another probable cause of arrhythmia could be a repeated electrical trauma accompanied by loss of consciousness. Since the cause of the disease was difficult to determine, the dilatation of the cardiac cavity detected after EchoCG with an elevated NT-proBNP level of up to 815 pg/ml against the background of a persistent bradyarrhythmia

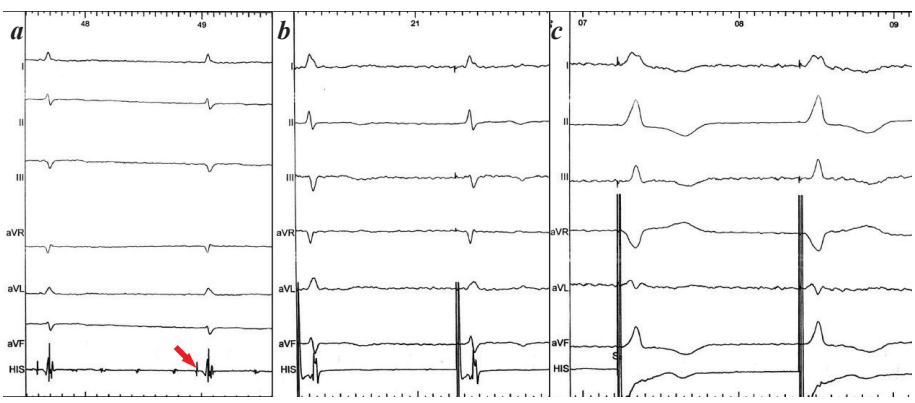

Fig. 4: a - intracardiac endogram of bundle branch area (arrow indicates bundle branch commissure), b - bundle branch stimulation, c - stimulation of RV septal area (endogram recording rate 67 mm/s, amplitude 10 mm/mV).

with a ventricular contraction rate of 40 per minute was considered to be a manifestation of arrhythmogenic cardiomyopathy. The validity of this interpretation is confirmed by the positive dynamics of the EchoCG data and the NT -proBNP level against the background of the continuous operation of the PM during the dynamic observation of the patient.

Besides the asymptomatic course, a long history of AF and AV block obviously plays an important role in the pathogenesis of arrhythmogenic cardiomyopathy. The absence of atrial systole against a background of AF and the presence of AV dyssynchrony with marked slowing of the heart rate is accompanied by a decrease in the atrial and ventricular contribution to LV filling in diastole. This leads to an increase in mitral regurgitation and occlusion pressure in the pulmonary artery, an increase in RV afterload, gradually leading to its dysfunction and enlargement, and dilatation of the fibrous rings of the tricuspid valve [5, 6].

Secondly, in this clinical example, a patient with an absolute indication for permanent PM implantation has opted for bundle branch pacing, which allows near physiological pulse propagation through the cardiac conduction system. It is known that the bundle branch is a part of the AV node whose stimulation leads to functional involvement of the left and right legs of the bundle branch without decrementing [7]. Implantation of an endocardial right ventricular lead in an apical position can lead to the occurrence and significant increase in tricuspid regurgitation [4, 8] with subsequent progression of right ventricular heart failure. Given the evidence of right ventricular dilatation with tricuspid regurgitation of moderate-to-severe on initial EchoCG in our patient, correct selection of the optimal area for intracardiac lead placement is critical to prevent progression of heart failure. PM implantation in the area of the bundle branch provides a normal sequence of ventricular contractions and does not dilate the QRS complex [8], as shown in our example. At the same time, a decrease in the diameter of the fibrous ring of the tricuspid valve against a background of hypotensive stimulation and normalisation of heart rate can be considered a predictor of local hemodynamic improvement (reduction in right ventricular preload). The stimulation of the bundle branch in the patient was thus accompanied by a positive dynamic in the form of a reduction in the size of the cardiac cavity, a normalisation of the LV myocardial mass index, a reduction in regurgitation at AV valves, especially at the tricuspid valve.

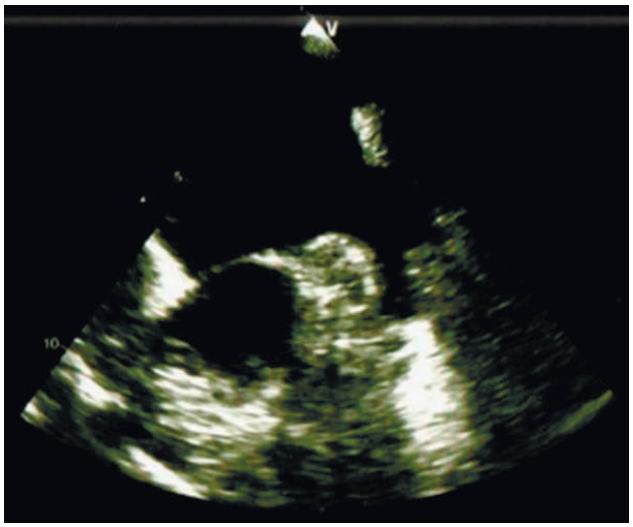

Fig. 5. No signs of thrombosis and spontaneous echocontrasting in LAA according to TOE.

Thirdly, this example shows a rather unusual situation where a soft spherical parietal thrombus was detected in LAA with signs of moderate spontaneous echocontrast and decreased velocity indices in LAA in a young patient with TOE. Possible cause of LAA thrombosis formation, first of all, can be the formation of cardiomyopathy of both atria [5, 6], and ventricles. In our previously published work, left atrial cavity dilatation and the presence of eccentric LV hypertrophy were independent echocardiographic predictors of LAA thrombosis in patients with non-valvular AF [9]. These changes are also observed in our patient and may be involved in the pathogenesis of thrombosis.

Another possible cause of thrombogenesis is an unreasonably low dose of dabigatran. According to the instructions and clinical guidelines, a standard dose of 150 mg 2 times daily should also be taken in combination with clopidogrel; there was no evidence to reduce the dose at the time of hospitalisation [10]. Considering the coagulation indices, we left dabigatran as is, but the dosage was increased to the standard dose of 150 mg twice daily.

One of the possible factors that also contributes to the earlier development and rapid progression of cardiovascular pathology (arterial hypertension) with the formation of thrombosis could be the negative effects of the climatic conditions of the far north. According to literature data, thermoregulatory adaptation to low air temperatures leads not only to vasoconstriction, increased BP, but also to fluid loss, increased blood viscosity without compensatory activation of the fibrinolysis system with subsequent development of hypercoagulation [11]. According to our previous retrospective study [12], in patients living in the far north, the presence of LV hypertrophy is one of the most important predictors of LAA thrombosis, and compared to mid-latitude residents, northerners show LV hypertrophy at an earlier age.

CONCLUSION

The clinical observation presented thus shows the combined effect of several unfavourable pathological factors in a young patient living in the far north, which led to the formation of arrhythmogenic cardiomyopathy, heart failure on a background of complex arrhythmias and the formation of a thrombus in LAA. Properly chosen therapeutic tactics to eliminate chronotropic insufficiency using stimulation of the bundle branch made it possible to achieve a positive dynamic in the form of reversed structural and functional cardiac remodelling and elimination of signs of heart failure, and administration of the standard dose of dabigatran resulted in lysis of the thrombus in LAA. Moreover, one cannot deny the possible additional influence of the unfavourable climatic conditions of living in the far north on the patient's body, which was the basis for the recommendation to change the place of residence to a region with a more favourable climate.

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