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Asymptomatic severe mitral regurgitation in patient with undifferentiated connective tissue dysplasia. Clinical case of timely diagnosis and successful treatment

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Abstract. The spectrum of mitral valve (MV) pathology in patients with connective tissue dysplasia (CTD) include conditions from myxomatous degeneration with excess tissue of the valve leaflets and subvalvular apparatus, which is more common among young patients, to fibroelastic deficiency of the MV leaflets that is usually diagnosed in older age groups. Mitral regurgitation (MR) in patients with dysplasia belongs to the category of primary MR that can progress and lead to surgical treatment.

It is known that surgical intervention on MV in patients with CTD is recommended in cases of symptomatic severe MR. In asymptomatic severe MR with such pathophysiological consequences as left ventricular systolic dysfunction, pulmonary hypertension, atrial fibrillation, surgical treatment is also indicated. The question of surgical treatment of asymptomatic severe MI without the mentioned above criteria remains controversial.

Using the clinical example of long-term observation of the asymptomatic severe MR we will present step-by-step algorithm for patients with severe primary MI considering the latest clinical guidelines on valvular heart disease of 2021.

Keywords: mitral valve, mitral regurgitation, mitral valve repair, mitral valve replacement, mitral valve dysplasia.

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Introduction

Primary MR is associated with pathology of the MV and/or its subvalvular structures in contrast to secondary MR due to left ventricular (LV) pathology or left atrial dilatation (LAD) in patients with atrial fibrillation (AF). The most common cause of primary MR is connective tissue dysplasia, known as MV prolapse (MVP), a degenerative MV disease. Cardiac auscultation and echocardiography are the main tools for the diagnosis of this pathology, accompanied by transesophageal echocardiography (TEE) and cardiac MRI in controversial cases.

The understanding of disease pathophysiology and timely use of effective MR surgery is essential for the management of patients with severe primary MR. The necessity of surgical treatment is assessed considering the severity of MR, size and function of LV, presence of pulmonary hypertension (PH), AF, correction possibilities by MV repair, and of course, disease symptoms. In the absence of complaints in patients with severe primary MR, it is difficult to decide whether to perform surgery or wait, and waiting will sooner or later lead to irreversible left ventricular dysfunction.

Rational management of such patients is based on the research data that are used to update the clinical guidelines for the management of valvular heart disease regularly.

Clinical case

Patient Ya., 36 years old. Heart murmur persisted since the age of 15, at the age of 18 he was diagnosed with severe MR in the background of MV prolapse. The patient had been annually observed for 10 years, but because of the absence of complaints and stable normal parameters according to echocardiography, he did not consult a physician afterwards. Over the last year he started to have increased heart rate (HR) at restthat was the urged him to cardiologist.

The patient had asthenic constitution (height 186 cm, weight 71 kg, BMI 20.5); auscultation revealed holosystolic murmur in the precardiac area within interscapular space. Cardiac rhythm was regular, apex beat was intensified. Six-minute walk test — 500 meters. ECG showed sinus rhythm.,signs of left ventricular (LV) myocardial hypertrophy.

To determine the strategy for management of MVP, it is necessary to confirm the clinical and auscultatory picture by visualization of the heart valves.

Echocardiography is a gold standard for the diagnostics of cardiac valve pathology [1, 2]; in case of MR it enables to estimate its presence and severity accurately, describe MV pathology (changes of leaflets, localization, mechanism of MR — tear or prolapse, etc), determine hemodynamic consequences of heart chambers volume overload. In controversial cases, echocardiography can be supplemented by stress echocardiography, transesophageal echocardiogram (TEE), cardiac magnetic resonance imaging (MRI) and cardiac computed tomography (CT) [3, 4].

Step-by-step follow-up of the clinical guidelines for the management of valvular heart disease helps a physician to identify MR, determine the stage of the disease and, based on the results of scientific research, improve long-term outcomes in asymptomatic patients with severe MR [5, 6], by choosing the optimal and well-timed treatment strategy.

Step 1: Assessment of MR severity is performed according to the criteria proposed by ACC/AHA [7, 8]. MR is defined by both qualitative and quantitative criteria. Criteria of MR, including severe, are presented in Table 1.

Step 2: Determination of etiology and mechanism of MR. In primary MR, the most frequent etiological cause is MVP (about 2% in the population) [9, 10]. The important point is to specify: whether one or both leaflets are affected, whether there is no rupture of subvalvular structures.

At this stage it is also essential to clarity whether the primary MR was due to fibroelastic deficiency, as in isolated MV prolapse, or is it the Barlow disease, when there is an excess of MV tissue. The later situation is considered in the case of both leaflets prolapse

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Table 1. **MR severity criteria**

	Severity	Mild	Moderate	Severe
Qualitative criteria	Assessment by coronary angiography	1+	2+	3–4+
	Color flow doppler	< 20% LA	Variable	Central > 40% LA or holosystolic eccentric flow through MV
Quantitative criteria	Vena Contracta	< 0,3 cm	0,3–0,69 cm	⩾ 0,7 cm
	Regurgitation volume, (ml/beat) RegVol	< 30	30–44 45–54	⩾ 60
	Regurgitation fraction RF (%)	< 30	30–39 40–49	⩾ 50
	Effective regurgitant orifice area ERO (cm^2)	< 0,2	0,2–0,39	⩾ 0,40

that will be important for subsequent surgical treatment of MR.

Step 3. Evaluation of cardiac chamber sizes and volumes, LV function, which change under the influence of volume overload due to severe MR [11, 12].

Step 4. Assessment of the disease stage (Table 2). At this point, it is important to determine the stage of the disease, since the patient, remaining asymptomatic in stage C (see Table 2), has compensated MR, and MV surgery can still improve patient's prognosis. In urgent stage D, MR correction is usually ineffective [13, 14].

What is known about prognosis of asymptomatic patients with severe primary MR? The chance of asymptomatic patient with severe MR not to have chronic heart failure (CHF) and AF within 5 years is 36% [15]; 30–40% of patients will need MV surgery within 5 years, and complications they will include CHF, AF, pulmonary hypertension (PH), stroke, ventricaular tachycardia/ventricular fibrillation (VT/VF), death. Non-operative mortality in asymptomatic patients with primary MR is 0–8.4% [15, 16].

There are data on outcomes and various markers in patients with asymptomatic severe primary MR:

Assessment of MR and ejection fraction (EF) has a great prognostic value. According to Enriquez-Serrano group, the more severe is the MR, the worse is the prognosis [17, 18]. In MR, left ventricular ejection fraction (LV EF) is "supernormal", i.e., EF over 60% is considered normal, and below 60% — below normal and should be a trigger for surgical intervention.

In a multi-centric study, Ling et al. demonstrated that MV subvalvular rupture is always characterized by worse prognosis than in a healthy population, and outcomes with early surgery are superior to medical treatment [19, 20].

Patients with severe primary MR accompanied by PH had worselong-term outcomes– pulmonary artery pressure (SPAP) less than 35 mm Hg did not affect the prognosis, and when it increased over 45 mm Hg, the long-term prognosis worsened [21, 22].

Additional markers in patients with severe MR — LV Strain and brain natriuretic peptide (BNP) [23, 24]. In the study of 548 asymptomatic patients with severe MR and preserved LV EFwithout indications for MR surgery, these markers were informative in a regard to the prognosis [18, 25].

According to the results of the study published in 2014, the stress test has prognostic value: 884 patients with severe MR and preserved LV EF were examined. Those patients who did not reach 85% of necessary load had worse prognosis. In 576 pa-

Table 2. **Primary MR disease stages**

Stage	Definition	Hemodynamic changes	Symptoms
A	Risk of MR	No	No data
B	MR progression	• Moderate enlargement of LA • No LV enlargement • Normal pressure in lung artery	No data
C	Asymptomatic severe MR	• Moderate or severe LA enlargement • LV enlargement • PH is present in resting state or during: physical activity — C1: LV EF > 60% and LVID < 40 mm — C2: LV EF ⩽ 60% and LVID ⩾ 40 mm	No data
D	Symptomatic severe MR	Moderate or severe LA enlargement LV enlargement PH	Reduced exercise tolerance Dyspnea during physical activity

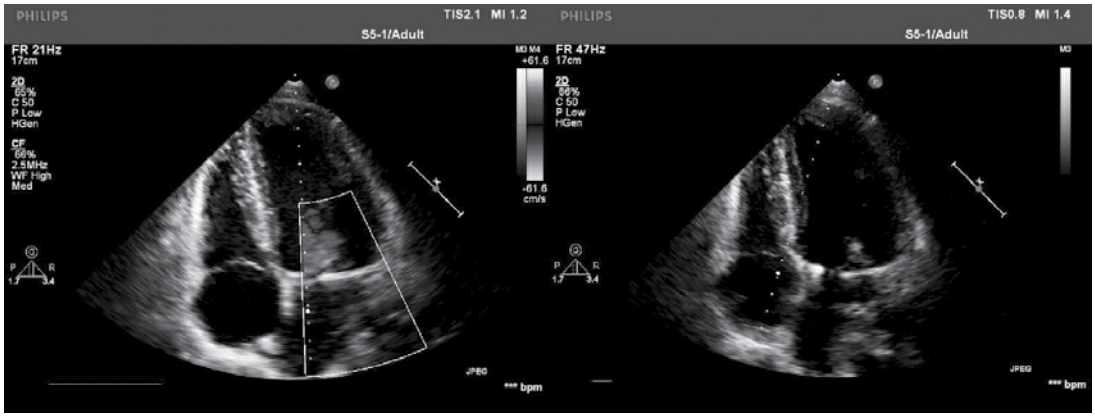

Fig. 1. Echo of the patient with severe MR before surgery

tients who performed over 100 % load, a refusal from MV surgery was not associated with a poor prognosis for at least five years [26].

Step 5. What are the indications for surgical treatment of severe primary MC in asymptomatic patients?

The latest 2021 Clinical Guidelines for the Management of Valvular Heart Disease of the European Society of Cardiology and Cardiothoracic Surgeons state that if the probability of successful MV repair is over 95 % and the estimated mortality of planned surgery is less than 1 %, surgical treatment should be performed in patients severe MR. It is especially important in the presence of PH, LV enlargement, LV EF decrease less than 60 % [27, 28]. According to above-mentioned guidelines, there should be very strong reasons not to perform surgery in these patients. One of such reasons can be insufficient experience of the surgical team, inability to guarantee the success of MV repair.

Summarizing the information above, the patient should undergo surgical treatment in case when severe MR is detected and there is no need to wait for the development of LV dysfunction and progression of clinical symptoms, and it is important to have an experienced surgical team that can offer wide range of surgeries on MV [29, 30].

Step 6. Cardiologist and the cardiac surgeon should inform patient on which MV surgery is and surgical incisions are planned.

Possible surgical approach options for surgical treatment of MR include total sternotomy, partial sternotomy, and anterolateral thoracotomy. There are many variants of MV repair and its combinations, and implantation of artificial heart valves is performed using both biological and mechanical prostheses. MV repair is preferable to mitral prosthesis in patients with isolated primary MR [4, 18], especially when using a mini-access.

Step 7. The key one, concerning the residual (return) MR and LV EF. Residual MR occurs infrequently, mainly after anterior MV leaflet repair, or the repair without using MM ring. The lower postoperative EF is, the worse are the outcomes [28].

Discussion

In the presented clinical case the patient underwent an echocardiography (Echo) (Fig. 1): the MV leaflets hadmyxomatous degeneration, there were anterior and posterior MV leaflets prolapse, dilation of the left LA, LV, MV fibrous ring. LV EF was 58 %, systolic pulmonary artery pressure (SPAP) was 39 mm Hg. Color flow doppler indicated the presence of eccentrically directed heavy MR flow. ERO — 0.45 cm^2, RV — 70 ml were calculated, which quantitatively confirmed the severity of the detected pathology.

According to the Echo results, the patient had severe asymptomatic MR in the background of Barlow disease, with hemodynamic overload of the left heart chambers, which has been going on all these years without affecting the patient's quality of life. Obviously, the had stage C, progressing MR, waiting for the appearance of clinical manifestation of the disease (stage D) is unacceptable, as it will worsen the patient's life prognosis and will not lead to the improvement of the condition after MV surgery, if it is postponed again (see Table 1).

On this basis, the patient was recommended to undergo MV repair with the installation of the support ring and it was explained that in case of unsatisfactory results, a prosthetic MV will be needed. Effective correction of the defect is evaluated intraoperatively, and if the MR persists, the patient is reoperated.

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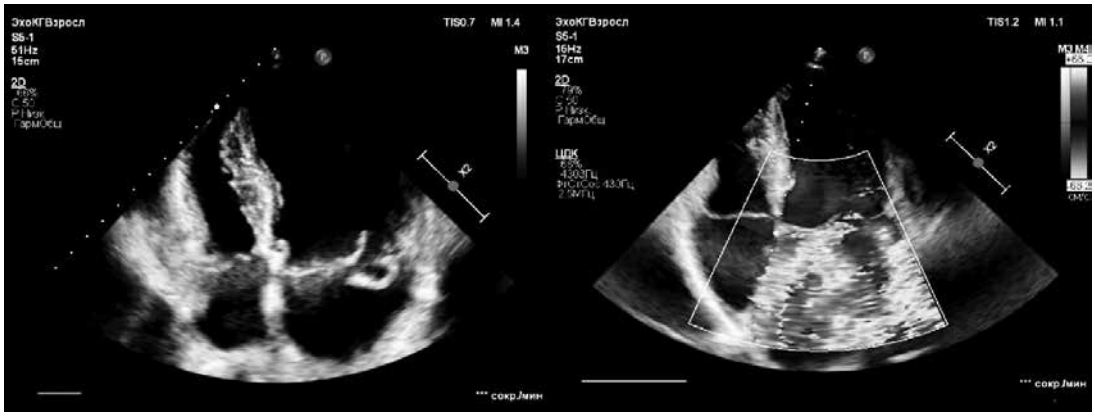

Fig. 2. ECHO of the patient after the surgery

In this clinical case the dilated MV fibrous ring was narrowed, it resulted in optimal coaptation of excess MV leaflet surfaces, providing an extended zone of contact between the anterior and posterior leaflets. One week after, by the time of discharge, due to the absence of volume overload, the size of LV and LV decreased, there were no residual MR, systolic anterior motion (SAM)-syndrome, EF was normal (Fig. 2). The patient was discharged in good condition.

Conclusion

The management of patients with severe primary MR should be performed in accordance with the current guidelines on valve diseases.

It is simple and clear to follow the algorithm when there are clinical manifestations of the disease and LV dysfunction; more difficult — when there are no symptoms. However, according to the 2021 guidelines, the earlier surgery is associated with better results.

The key point of the diagnosis is accurate Echo data. In addition, the role of biomarkers, stress test, and LV Strain is important.

The decision-making team regarding surgical treatment of MR should discuss all cases of severe primary MR, recommend the best time for surgery, suggest advanced valve repair techniques, and present their own experience and success in this direction.

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