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VENTRICULAR ARRHYTHMIAS IN A CHILD WITH MARFAN SYNDROME: CASE REPORT

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We present a severe disease progression observed in a 13-year-old patient diagnosed with Marfan syndrome and associated cardiac rhythm disorders, including polymorphic ventricular premature contractions and persistent ventricular tachycardia resistant to a wide range of antiarrhythmic medications. We conducted an analysis of contemporary perspectives on the etiology of ventricular tachyarrhythmias and their impact on the prognosis of patients with Marfan syndrome. Conclusions were drawn regarding the selection of treatment strategies for this specific patient population.

Key words: Marfan syndrome; ventricular premature contractions; ventricular tachycardia; cardiomyopathy; *FBN1*; fibrillin-1; propranolol; amiodarone

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Marfan syndrome is a rare autosomal dominant connective tissue disorder characterized primarily by abnormalities affecting the cardiovascular and musculoskeletal systems, as well as ocular manifestations. The incidence of Marfan syndrome according to different data is 1:5000-20000 people [2, 3]. The molecular genetic basis of the disease is mutations in the *FBN1* gene, which are detected in 70-93% of cases [4]. Fibrillin-1 protein is the main structural component of microfibrils, normally providing contractility and elasticity of connective tissue. Due to the disruption of the structure of this protein in people with Marfan syndrome, connective tissue becomes more stretchable and less strong [5].

To date, it is believed that cardiovascular pathology is a major determinant of life expectancy in patients with Marfan syndrome [6]. The most frequent cardiovascular disorders are dilatation of the ascending aorta, mitral valve prolapse and pulmonary dilatation [7]. While ascending aortic dilation reliably correlates with the onset of life-threatening conditions such as aortic wall dissection and rupture, the impact of ventricular heart rhythm disorders (VHRD) on the prognosis of individuals with Marfan syndrome remains incompletely elucidated. Thus, in a study by Anji T. Yetman and colleagues, it was shown that death due to arrhythmogenic events occurred in 4% of cases, and the presence of VHRD was associated with unfavorable prognosis for patients [8]. However, according to other studies, unstable ventricular tachycardia (VT) is not a definitive predictor of sudden cardiac death (SCD) [9, 10].

It is widely acknowledged that a predisposing factor to the development of left ventricular dysfunction in patients with Marfan syndrome is cardiac surgery and the resulting hemodynamic overload of the left ventricle (LV) [11, 12]. Increased LV size and increased NT-proBNP levels are significantly correlated with the likelihood of VHRD [8-10, 13]. However, in addition to recognizing heart failure as a cause of VHRD, there is an increasing body of evidence suggesting possible primary myocardial damage in patients with Marfan syndrome. This includes the presence of a specific cardiomyopathy in patients with Marfan syndrome and Marfanoid appearance, attributed to myocardial remodeling due to dysregulation of transforming growth factor-beta (TGF-β) and hemodynamic stress acting on structurally defective connective tissue. These factors contribute to the development of arrhythmias [11, 12, 14, 15]. For example, in a study by A.S. Rudoy et al., which included 23 patients with Marfan syndrome,

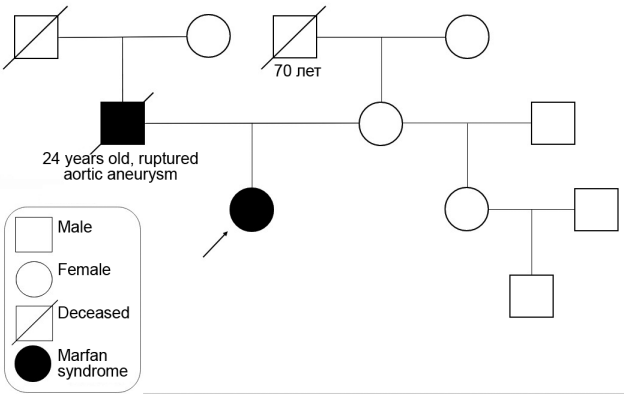

Fig. 1. A graphic representation of the proband's pedigree.

echocardiography (Echo) revealed signs of cardiomyopathy development, such as decreased ventricular systolic function, increased isovolumic relaxation time, and the development of left ventricular diastolic dysfunction [16].

The choice of the amount and type of therapy in patients with Marfan syndrome in the presence of VHRD is currently a difficult task. According to a number of studies, drug antiarrhythmic therapy (AAT) may be ineffective, and consideration should be given to the feasibility of implantation of a cardioverter-defibrillator to prevent the development of life-threatening arrhythmogenic events [11]. The presented clinical case demonstrates the development of severe VHRD in a pediatric patient with Marfan syndrome without prior cardiac surgery.

Clinical case

From the medical history, it is noted that the girl is from the seventh pregnancy, during which she experienced a threat of termination of pregnancy in the third trimester, occurring against a background of mild iron deficiency anemia. The delivery was term, independent, the period of adaptation was favorable. Hereditary history is aggravated, her father died of a ruptured aortic aneurysm at the age of 24 years and was retrospectively diagnosed with Marfan syndrome. The medical pedigree is summarized in Fig. 1.

When examined by a pediatrician at the age of 3 years, the child was heard a systolic murmur at the apex of the heart, and consultation with a cardiologist was recommended. Echo revealed signs of myxomatous degeneration of mitral valve flaps, aortic dilation at the level of Valsalva sinuses up to 3 cm. Therapy with bisoprolol 0.1 mg/kg/day was prescribed.

At the age of 5 years, when complaints of visual impairment appeared, due to the presence of phenotypic features, aggravated family history, the child was examined in hospital, where the diagnosis of «Marfan syndrome» was established. Echo data showed borderline cardiac ventricular dimensions, moderate mitral valve insufficiency, dilation of the root and ascending part of the aorta. Complex therapy with metoprolol, spironolactone, renin-angiotensin-aldosterone system inhibitors was prescribed. Dynamic examination in a multidisciplinary hospital revealed musculoskeletal disorders in the form of scoliosis, flat feet, and chest flattening. An ophthalmologist diagnosed a subluxation of the lens.

The heart rhythm disorder in the form of rare monomorphic ventricular extrasystole (VE) was first registered during routine examination according to Holter monitoring at the age of 9 years, and rapidly progressed with increasing representation and density of ectopic activity. Thus, at the age of 10 years, the representation of ventricular ectopy was 38%, with polymorphic VEs recorded, as well as rare runs of erratic VT and prolongation of the QTc interval up to 545 ms. AAT selection was performed with sequential evaluation of the efficacy of such drugs as bisoprolol, sotalol, atenolol, and propafenone at age-appropriate dosages. The best therapeutic effect was achieved against the background of propafenone 10 mg/kg/day, however, several years after the beginning of administration, depletion of the drug effect was observed, in connection with which propafenone was replaced by lappaconitine hydrobromide, which, in turn, was discontinued six months after the beginning of administration due to recurrence of ectopy.

At the age of 13 years, the girl was first admitted to the pediatric cardiology department of cardiac rhythm disorders of the Clinical Research Institute of pediatrics and pediatric surgery. She complained of visual impairment, occasional back pain, otherwise her health was not affected. On objective examination: the individual exhibits high physical development, with an asthenic physique characterized by a deficit of body weight relative to height. Physical findings include kyphoscoliosis, flat feet, arachnodactyly, ec-

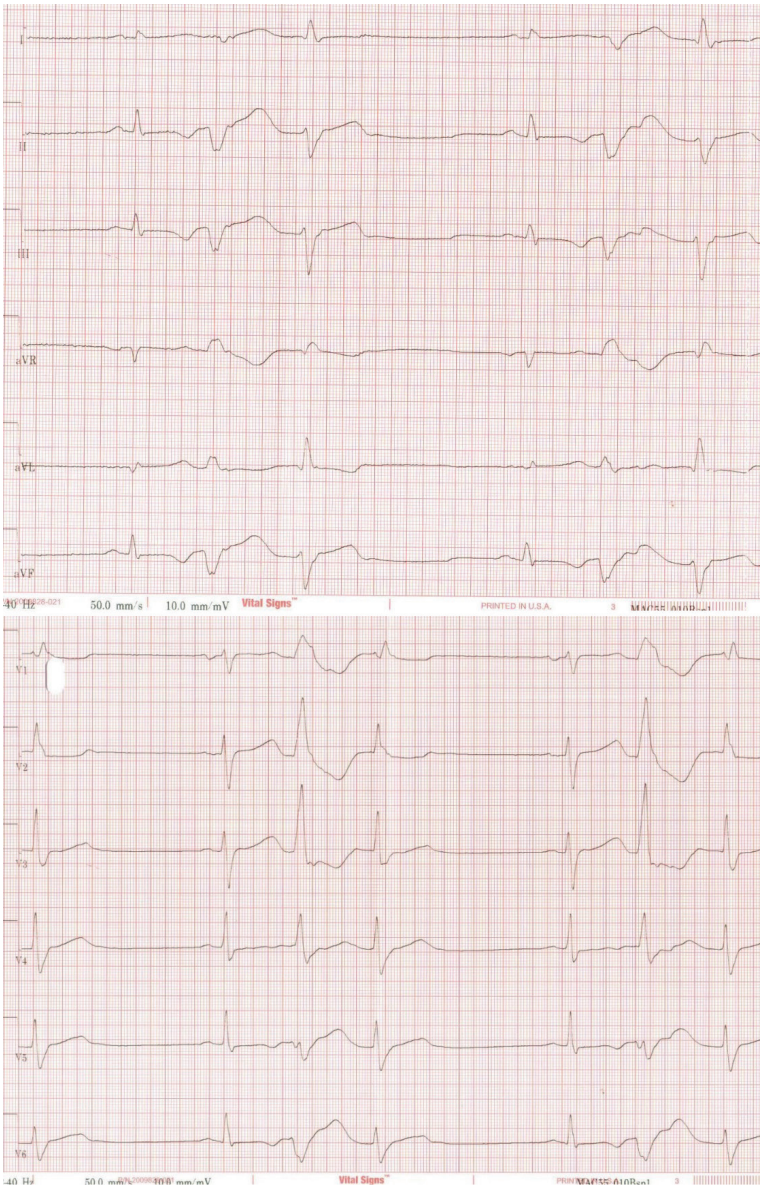

Fig. 2. A fragment of an ECG recording.

topia of pupils, asymmetric chest deformity, and a high palate. On auscultation of the heart, a 2/6 grade systolic murmur was noted at the apex of the heart. The individual's heart rate (HR) was 51 beats per minute, and blood pressure (BP) measured 95/55 mm Hg. General blood analysis and urinalysis yielded unremarkable results. In blood biochemical study, moderate increase of natriuretic peptide level up to 140 pg/mL (norm <100 pg/mL), CPK-MB up to 2.3 ng/mL (norm up to 2.0) attracted attention. ECG showed sinus bradycardia, polymorphic VE, QTc interval prolongation up to 481 ms (Fig. 2). According to Holter monitoring data: sinus rhythm, average HR within normal limits (91/74/78 beats/min). Heterogeneity of repolarization processes with periodically pronounced U tooth. Ventricular ectopic activity was registered in the form of single, paired polymorphic VEs (presumably from LV), short paroxysms of poly- and monomorphic VT with HR up to 176 beats/min with total representation of ventricular ectopy 43.3%. The mean corrected QT interval over a 24-hour period was 453 ms.

According to the treadmill test, polymorphic VE, unstable polymorphic VT on recovery (Fig. 3), and QTc interval prolongation (466 ms / 467 ms / 480 ms at outcome, peak exercise, and recovery, respectively) were recorded throughout the study. Echo visualized dilation of the aortic base (3.8Z), ascending aorta (2.45Z), sinuses of Valsalva (3.5Z), and late-diastolic aortic regurgitation 1+ (Fig. 4). LV cavity dilation (end-diastolic volume 138-142 ml (N for weight and height up to 102 ml), end-diastolic volume index up to 86 ml/m^2 (N for weight and height up to 75 ml/m^2), end-diastolic diameter 61-62 mm (Z-score 2.92)), relatively small thickness of myocardium of the inferior, posterior and lateral walls (up to 4 mm), microdiverticula at the base of papillary muscle attachment of the posterior group, scattered type of papillary muscle structure (many thin muscle bundles), transitioning to wall trabecularity at the level of middle and apical segments, increased trabecularity. Dilation of the mitral valve fibrous annulus (2.94Z), myxomatosis and prolapse of mitral valve flaps up to 9-11 mm, moderate regurgitation (Figure 5). Severe tricuspid regurgitation. The Teicholz LV ejection fraction was 58% (at the lower limit of normal), diastolic function of both ventricles was not impaired.

Combined AAT with atenolol (0.8 mg/kg/day) and amiodarone at a dose of 6.8 mg/kg/day (400 mg daily) was prescribed. Control Holter monitoring revealed a decrease in ectopic activity to 9%, but due to prolongation of the QTc interval to 505 ms, regarded as secondary changes on the background of AAT, the dose of amiodarone was reduced to 3.4 mg/kg/day (200 mg per day). In the course of Holter monitoring six months after the administration of combined AAT, the low efficacy of AAT was demonstrated; therefore, the non-selective beta-adrenoblocker propranolol 1 mg/kg/day was administered, with moderate positive dynamics in the form of absence of unstable VT during six months from the beginning of therapy.

*The patient underwent molecular genetic study, and the targeting regions of the human clinical exome were investigated. In exon 43 of the FBN1 gene, a nucleotide variant c.5279_5284delinsTACCC in heterozygous state resulting in a p.Y1760Lfs*133 reading frame shift was detected, considered as probably pathogenic.*

DISCUSSION OF FINDINGS

Aortic root dilatation and dissection remain the leading causes of death in patients with Marfan syndrome, and heart failure and SCD due to life-threatening VHRD are considered as additional factors [11]. When analyzing studies of the last decades, it was noted that mortality associated with aortic lesions is decreasing due to improved approaches to diagnosis and treatment, while the importance of heart failure and heart rhythm disorders is increasing [12].

In the absence of undergone cardiac surgical interventions, the presence of VHRD is usually associated with dilatation of the heart chambers. Specialists have suggested the possibility of using such indicators as increased LV dimensions and increased levels of brain natriuretic peptide as predictors of the risk of VHRD development. In D.Y.Mah et al. materials, a higher index of LV end-diastolic size (with Z-score), accompanied by echocardiographic signs of mitral regurgitation in 83% of cases, was noted in patients with VHRD [13]. Nevertheless, hemodynamic overload in isolation cannot explain the presence of structural cardiac changes in a number of patients. Thus, in the study by A.T.Yetman et al. a reliable association between the development of VHRD and dilation of heart chambers was also determined; however, mitral insufficiency was observed in only 21% of patients [8]. Based on the results of several studies, a significant role of specific Marfan cardiomy-

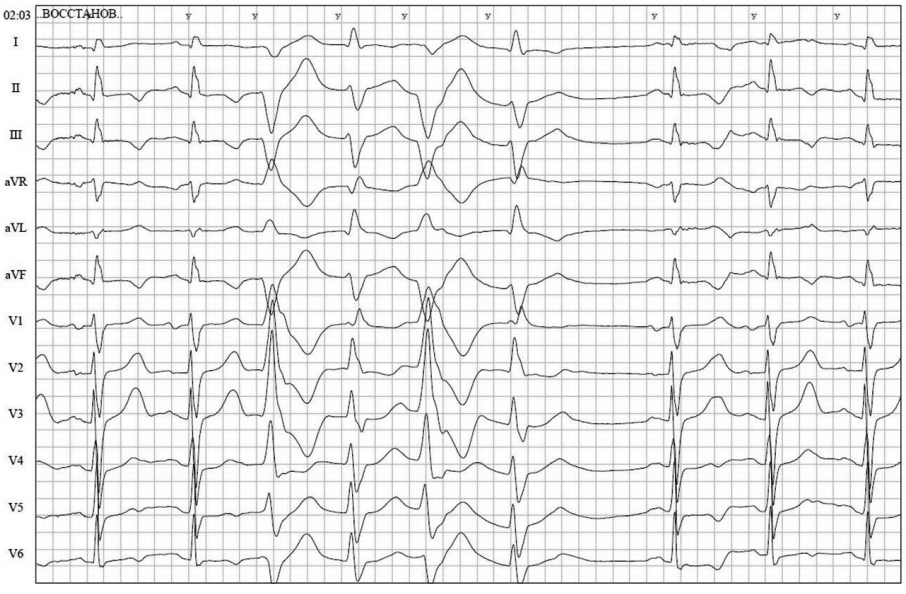

Fig. 3. Unstable polymorphic ventricular tachycardia during the treadmill test.

opathy in the genesis of cardiac cavity enlargement and reduced systolic function, and consequently in the development of heart rhythm disorders can be concluded [11, 12, 14, 17].

In the presented clinical case, the patient had no significant mitral regurgitation that could explain the cavity dilatation, which allowed us to consider the specific Marfan cardiomyopathy in this child as the main cause of dilatation. In the biochemical study of blood there was an increase in cerebral natriuretic peptide up to 140 pg/mL, which is highlighted by a number of authors as a reliable predictor of the development of VHRD. Although there are studies devoted to this issue, the exact determination of the proBNP threshold value remains an unsolved problem [9, 18]. In a prospective study by B.A.Hoffmann et al. including 77 patients with Marfan syndrome with a mean follow-up period of 3 years, a significant relationship was found between an increase in NT-proBNP level of more than 214.3 pg/mL and the risk of arrhythmogenic events such as SCD, VT, ventricular fibrillation or arrhythmogenic syncope [9].

Selection of AAT in patients with Marfan syndrome is currently challenging. In our clinical observation, the ectopic activity was resistant to a wide range of drugs, including combined AAT. In addition, the presence of a prolonged QTc interval significantly limits the use of AAT, increasing the risks of proarrhythmogenic effects of therapy. The low efficacy of beta-adrenoblockers to suppress VHRD in patients with Marfan syndrome was shown earlier in the work of A.T.Yetman and colleagues [8, 11].

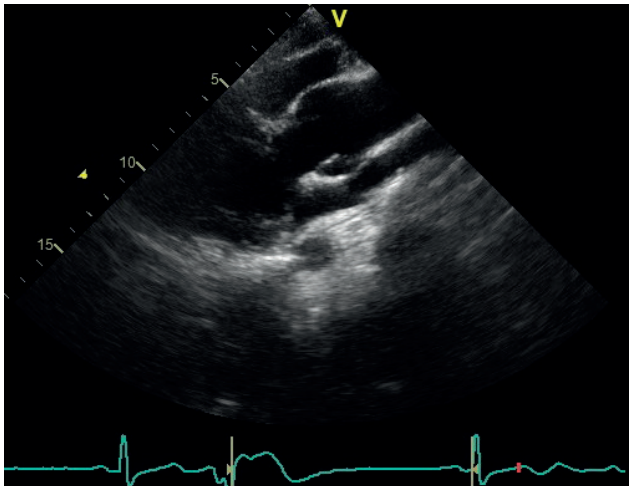

Fig. 4. B-mode echocardiogram: aortic dilation at the level of the sinuses of Valsalva.

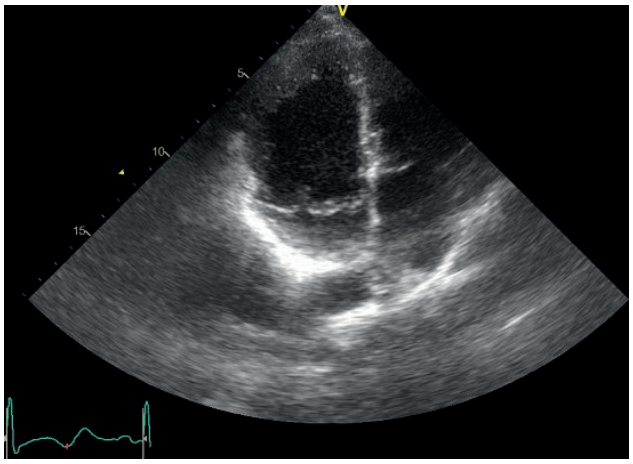

Fig. 5. Echocardiogram in B-mode: mitral valve prolapse.

The problem of appropriateness of implantation of a cardioverter-defibrillator in patients with Marfan syndrome and VHRD is based on the risk stratification of SCD due to arrhythmogenic causes. The results of studies investigating the relationship between the presence of ventricular ectopy and the development of SCD are conflicting. Thus, in the observation of A.T.Yetman et al. including 70 patients with Marfan syndrome with a mean follow-up period of 6 years, it was shown that ventricular ectopy (VE and unstable VT) was an independent risk factor for SCD, and 4% of patients died due to the development of life-threatening rhythm disturbances [8]. Also in favor of an unfavorable prognosis in patients with Marfan syndrome when ventricular ectopy is registered are the data obtained from the analysis of the national database of patients observed in hospital settings for 10 years (from 2004 to 2015). The study included 12079 patients, including 1691 patients under the age of 18 years. VT occurred in only 1.7% of cases, but these patients had the highest in-hospital mortality rate of 5.3% [19].

In addition to recognizing ventricular ectopy in patients with Marfan syndrome as an independent predictor of the development of SCD, there is an opposing viewpoint based on the results of both retrospective and prospective studies. Thus, in the work of B.A.Hoffmann et al. including 77 patients, as well as in the work of A.Aydin et al. including 80 patients, when attempting to apply the presence of VHRD as a risk criterion for SCD, no reliable association was obtained. Thus, the issue of stratification of the risk of SCD occurrence in patients with signs of VHRD remains open and requires further study [9, 10].

CONCLUSION

Close monitoring of heart rhythm abnormalities is required in patients with Marfan syndrome, including those without prior cardiac surgery. Determination of the genesis of VHRD requires a detailed analysis of the examination data in dynamics. The presence of VHRD may be attributed to existing structural changes in the ventricular myocardium, such as the presence of microdiverticula, heterogeneity of myocardial structure with thinning zones, etc. This is particularly evident when the presumed localization of ventricular ectopy coincides with the zone of myocardial changes. If there is a correlation between the progression of ventricular cavity dilatation, increased NT-proBNP levels, decreased myocardial contractile function, and ventricular ectopy, specific Marfan cardiomyopathy should be considered as a potential cause of the heart rhythm disturbance. Further studies are needed to develop algorithms for the management of patients with Marfan syndrome and VHRD, to stratify the risk of SCD development and to determine the indications for implantation of a cardioverter-defibrillator in this group of patients.

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