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CARDIOVASCULAR REHABILITATION IN A CLINICAL CASE OF A PATIENT WITH MARFAN SYNDROME

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Abstract
Marfan syndrome is a genetic connective tissue disorder with autosomal dominant inheritance, caused by a mutation in the gene encoding for fibrillin 1 (FBN1), located on chromosome 15. This mutation causes excessive secretion of the transforming growth factor beta (TGF-beta), causing changes in connective tissue throughout the body - multisystemic disease (especially affecting the eye, cardiovascular and musculoskeletal level).
We hereby present the case of a 24-year-old male patient, diagnosed with Marfan syndrome, that was admitted in the Cardiovascular Rehabilitation Clinic of the Clinical Rehabilitation Hospital from Iași, Romania, for cardiovascular recovery after a surgical intervention for aortic dissection, performed through the Bentall procedure.
Keywords*: Marfan syndrome, cardiovascular recovery****.***

Rezumat
Sindromul Marfan este o boală genetică a țesutului conjunctiv, transmisă autozomal dominant, cauzată de o mutație în gena ce codifică fibrilina 1 (FBN1), situată pe cromozomul 15. Această mutație determină secreția excesivă a factorului de creștere transformator beta (TGF-beta), determinând modificări ale țesutului conjunctiv de la nivelul întregului organism-afecțiune multisistemică (în special la nivel ocular, cardiovascular și musculoscheletal).
Prezentăm cazul unui pacient în vârstă de 24 de ani, cunoscut cu sindrom Marfan, care a fost internat în secția de Recuperare Cardiovasculară a Spitalului Clinic de Recuperare, Iași, România, pentru recuperare cardiovasculară post intervenție chirurgicală pentru disecție de aortă, folosindu-se procedeul Bentall.
Cuvinte cheie*: sindrom Marfan, recuperare cardiovasculară.*

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Introduction

In 1896, the French pediatrician Antoine-Bernard Marfan presented the case of a 5-year-old girl exhibiting a series of characteristics specific to Marfan syndrome. In 1968, Hugh Bentall executed the procedure that is now named after him, substituting the ascending aorta and aortic valve in a patient diagnosed with Marfan syndrome. In 1991, Francisco Ramirez identified the gene whose mutations result in Marfan syndrome[1].

Marfan syndrome is a genetic disorder affecting connective tissue, characterized by mutations in the FBN1 gene, which encodes the protein fibrillin-1.

This protein is crucial for the formation of elastic fibers found in connective tissue [2,3]. The disorder affects multiple organs, mainly involving musculoskeletal, cardiovascular, and ocular systems. The prevalence of Marfan syndrome is approximately 1 in 5,000 individuals globally[4].

The syndrome presents a broad clinical picture due to its multi-systemic involvement. In the skeletal system, individuals often exhibit arachnodactyly, characterized by long, slender fingers and toes, and dolichosteno-melia, where the limbs are disproportionately long compared to the trunk. Other common skeletal features include pectus excavatum (sunken chest), pectus carinatum (protruding chest), scoliosis (abnormal curvature of the spine), joint hypermobility (excessive flexibility of joints), and a high-arched palate that often results in crowded teeth[5,6].

The ocular system is significantly affected in Marfan syndrome, with ectopia lentis (dislocation of the lens in the eye) being a hallmark feature, observed in about 60% of affected individuals. Other ocular complications include myopia (nearsightedness) and an increased risk of retinal detachment due to structural weaknesses in the eye[7].

Cardiovascular complications are the most life-threatening aspects of Marfan syndrome. Aortic root dilatation, which involves the enlargement of the base of the aorta, can lead to aortic dissection or rupture if not managed properly.

Additionally, individuals may experience mitral valve prolapse, where the valve between the heart's left atrium and left ventricle does not close properly, and aortic regurgitation, which involves the backflow of blood from the aorta into the left ventricle due to aortic valve insufficiency[8].

Marfan syndrome can also impact the pulmonary system, leading to conditions such as spontaneous pneumothorax (collapsed lung due to air leakage into the chest cavity) and restrictive lung disease, which arises from skeletal abnormalities affecting the chest wall.

The cutaneous system is also involved, with affected individuals often developing skin striae (stretch marks not associated with

weight changes), and recurrent hernias due to connective tissue weakness[5].

Diagnostic Criteria

The diagnosis of Marfan syndrome is primarily clinical and is based on the revised Ghent nosology criteria updated in 2010. These criteria place significant emphasis on aortic root aneurysm and ectopia lentis. Major diagnostic criteria include aortic root dilatation, defined by a Z-score ≥ 2 or evidence of aortic dissection, and ectopia lentis, which is verified through slit-lamp examination. Family history also plays a crucial role, with a confirmed first-degree relative with Marfan syndrome significantly supporting the diagnosis [9]. In addition to these major criteria, a systemic score based on a combination of skeletal, ocular, skin, and cardiovascular features is used. A systemic score of ≥ 7 is considered diagnostic in the absence of a family history. Genetic testing for the identification of a pathogenic FBN1 mutation can support the diagnosis, particularly in borderline cases[9,10].

Management of Marfan syndrome requires a multidisciplinary approach to address the various affected systems. Cardiovascular management is paramount, given the life-threatening nature of aortic complications. Beta-blockers are commonly prescribed to reduce the rate of aortic dilatation and lower the risk of aortic dissection. Angiotensin II receptor blockers (ARBs), such as losartan, have also been shown to decrease aortic root growth [11, 12]. Surgical intervention, such as aortic root replacement surgery, is indicated when the aortic root diameter exceeds 5.0 cm or if there is rapid progression[8].

Ocular management involves regular ophthalmologic examinations to monitor and manage ectopia lentis and other ocular complications. Surgical correction may be necessary for lens dislocation and severe myopia [7]. Skeletal management includes regular orthopedic surveillance for scoliosis and pectus deformities, physiotherapy and bracing to manage scoliosis and prevent progression, and surgical intervention in severe cases. Pulmonary management requires monitoring for pneumothorax and prompt treatment for lung complications[5].

Genetic counseling is an essential component of managing Marfan syndrome, providing affected individuals and families with information on inheritance patterns and reproductive options. This counseling helps families make informed decisions and plan for the future[13,14].

Clinical case presentation

We present the case of a 24 years old male patient that was admitted by direct transfer from the Institute of Cardiovascular Diseases "Prof. Dr. George I.M. Georgescu" Iasi for cardiovascular rehabilitation after a surgically intervention for aortic dissection.

From its medical history, we note that the onset of the current disease occurred in 2012, when he was diagnosed with Marfan syndrome complicated with ascending aortic aneurysm and subluxation of lens which was subsequently operated. In May 2024, he was admitted for Stanford A aortic dissection, giant ascending aortic aneurysm, cardiogenic shock, severe aortic insufficiency, aortic bicuspidy, moderate mitral regurgitation, moderate tricuspidian regurgitation, NYHA Class IV chronic heart failure with severely diminished ejection fraction and sinusal tachycardia. He was operated immediately by practicing surgical cure of the aortic dissection using the Bentall procedure, replacing the ascending aorta with a valvulated conduct.

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The reason for his admission in the Cardiovascular Rehabilitation Clinic of the Clinical Rehabilitation Hospital from Iași, Romania, was the postoperative cardiovascular recovery.

The objective physical examination revealed a conscious, cooperative patient, hemodynamically stable, BP:87/64 mmHg, HR: 117bpm, underweight, with marfanoid appearance, asthenic built (H:197cm). His teguments were pale and dry, with a presternal postoperative scar healing. The subcutaneous fat tissue was reduced. The muscular system was hypotonic, hypotrophic, hypokinetic (fig.1 and fig.2).

The osteoarticular system examination revealed a dorsal kyphosis (fig.3), arachnodactyly, ligamentous hyperlaxity (fig.5), pectus excavatum (fig.4 and fig.2), low upper/lower body ratio and increased anvergure/height ratio.

On his cardiovascular system examination we discovered: pectus excavatum, the precordial area with healing postoperative scar, apexian shock in the fifth left intercostal space in the midclavicular line, rhythmic heart sounds, tachycardia, with metallic click opening in the aortic focus.

The EKG reveals: sinusal tachycardia, HR: 117/min, QRS-left deviation, left ventricular hypertrophy, Socolov-Lyon index 40, bifid P waves (as dilatation), negative T waves in V1-V3 (fig.6).

Biological tests revealed leukocytosis with neutophilia, anemia and inflammatory syndrome (ESR 58mm/h, CRP:1.35mg/dl), hyposideremia and INR 5.23.

The cardiac ultrasound showed: LVDd 80 mm, LVDs76 mm, IVSd 16 mm, LVWd 14 mm, VTDVS 216 ml, VTSVS 165 ml, LA 43 mm, RVDd 27 mm, Ao asc 30 mm, E-A fusion, dPmax Ao 10 mmHg, Vmax Ao 1.6 m/s, dPmax tricuspid 17 mmHg, TAPSE 9 mm. Global cardiac dilation. Dilated and hypertrophied left ventricle with severely diminished systolic function, EF vol 24%. Dyskinetic IVS, otherwise diffuse hypokinesia of the LV walls. Normal functioning aortic metal prosthesis. Prosthetic duct ascending aorta. Improbable pulmonary hypertension. Severe systolic dysfunction on RV. Pericardial effusion 4mm behind LV (fig.7).

The patient received drug therapy, during the hospitalization, with: Furosemide 40 mg/day in the morning, Spironolactone 25 mg/day at lunch, Dapagliflozin 10 mg/day, in the morning, Digoxine 0,25 mg 1/2cp/day, at lunch, Carvedilol 3,125 mg/day, in the morning, Sacubitril/ Valsartan at BP >110mmHg 24/26mg/day, in the morning, Acenocoumarol 1mg/day, at lunch. He also benefited from cardiovascular kinetotherapy, local treatment of the postoperative wound and suppression of sutures.

During the hospitalization, the patient's evolution was favorable, with good tolerance during kinetotherapy, but the prognosis is

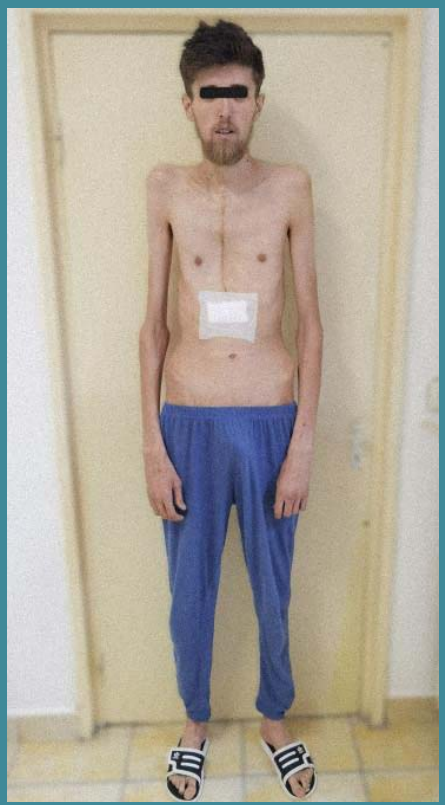

Figure 1. *Marfanoid appearance*

Figure 3. *Marfan syndrom-dorsal kyphosis*

Figure 2. *Marfanoid appearance*

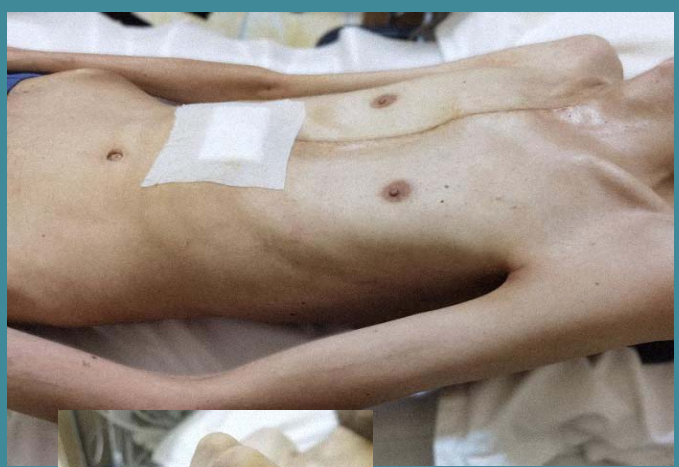

Figure 4. *Pectus excavatum, presternal postoperative scar healing*

Figure 5. *Arachnodactyly (positive thumb sign)*

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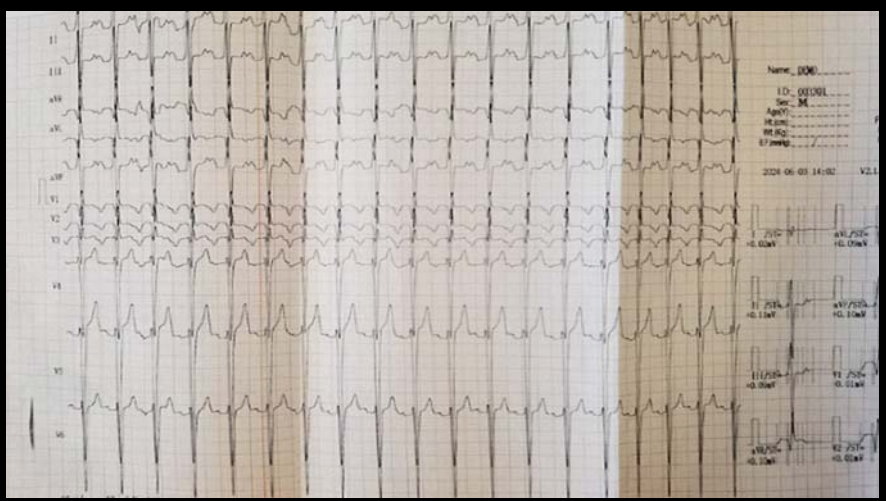

Figure 6. *Patient's EGK evaluation*

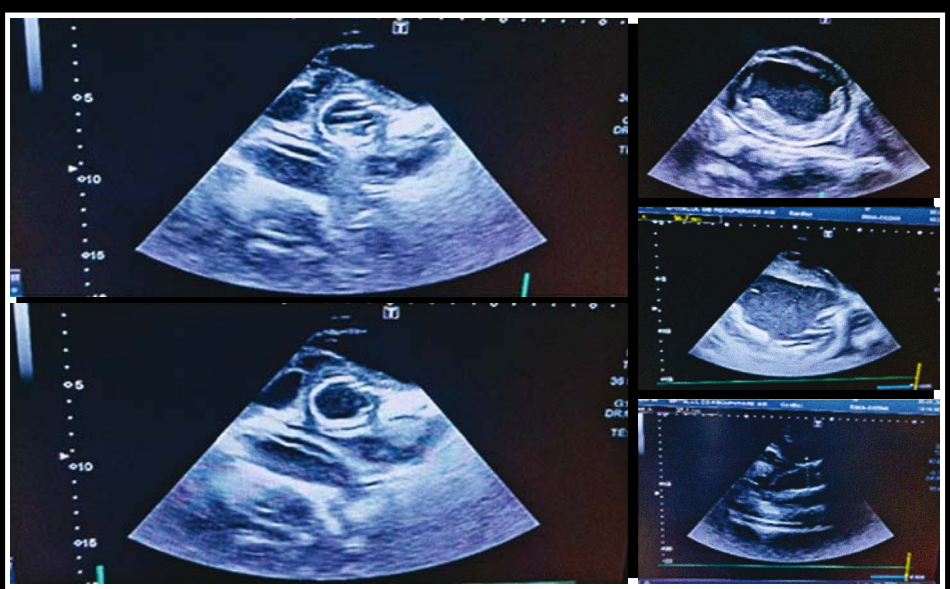

Figure 7. *Patient's cardiac ultrasound*

reserved due to the chronic heart failure with severely diminished EF.

He was discharged with the following recommendations: hyposodate, hypolipidic diet, to avoid intense physical efforts and extreme temperatures, smoking and alcohol consumption are prohibited, permanent medical treatment, coagulation control at 2 weeks with optimal INR 2.5-3.5, antibiotic prophylaxis of bacterial endocarditis prior to any major surgical or dental maneuvers, prohibition of intramuscular or subcutaneous injections, being allowed only intravenous injections, and periodic cardiological control.

Discussions

The case is notable due to the absence of a family history of Marfan syndrome in the patient, suggesting the possibility of a de novo mutation, which accounts for one of four cases. To confirm this, him and his family must undergo DNA testing, especially because Marfan syndrome is a genetic disorder with variable expressivity and first-degree relatives are at risk of being in fact affected, but not diagnosed yes. Being a young person, he should address for genetic counselling, in view of family planning.

Upon diagnosis, the patient presented with cardiovascular complications, specifically an aneurysm of the ascending aorta that progressed to aortic dissection, as well as ocular complications.

Awareness of the clinical signs of cardiovascular complications in patients, along with knowledge of surgical interventions, has demonstrated life-saving potential. The patient responded effectively, remaining calm and aware of the symptoms, thereby conserving valuable time with a timely arrival at the emergency room.

Individuals with Marfan syndrome should receive multidisciplinary counseling prior to pregnancy due to the increased risk of aortic complications, particularly when the aortic root diameter exceeds 4.0 cm. Some may elect prophylactic aortic root repair before pregnancy to reduce the risk of ascending aortic dissection, though this does not eliminate risks involving the descending aorta or other cardiovascular complications. Throughout pregnancy, efforts should be made to minimize cardiovascular stress. Close surveillance by a high-risk obstetrician is essential, with echocardiographic monitoring every two to three months and into the postpartum period, given the ongoing risk for aortic dissection. Beta-blockers should be maintained during pregnancy, while medications such as ARBs must be discontinued due to fetal risks. The mode of delivery—controlled vaginal birth versus cesarean section—should be individualized based on clinical factors, as there is no clear consensus[9,15].

Recently published articles demonstrated the importance of cardiovascular rehabilitation in patients with Marfan syndrome, increasing their quality of life and cardiovascular/muscular metrics, all of the above without affecting the aortic root diameter. Consequently, these patients require a comprehensive clinical assessment, and cardiovascular rehabilitation must be an essential component of their management strategy [16].

The patient's eligibility for a potential cardiac transplant may be questioned due to significant heart failure with reduced ejection fraction, which is critical for improving prognosis and life expectancy[15].

Conclusions

No specific treatment exists for Marfan syndrome yet. The management and care of these patients require the cooperation of a multidisciplinary team. Cardiovascular monitoring is paramount: it involves lowering blood pressure, avoiding strenuous physical

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activity, and surgical intervention may be life-saving.

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