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Difficulties in Diagnosing Marfan Syndrome in Rheumatologist Practice

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Abstract: Early diagnosis and timely therapy vascular complications of Marfan syndrome are extremely important - they determine the prognosis of patients' lives. Early cardiac surgical correction for Marfan syndrome allows significantly increase duration and improve quality of life of patients. Material and methods: Clinical laboratory-instrumental examination of patients diagnosed with Marfan syndrome. Results: A comprehensive examination aimed at searching for characteristics of Marfan syndrome and hereditary connective tissue disorders indicated for first-degree relatives with the purpose of early diagnosis and correction of possible anomalies. Conclusions: This clinical case deserves attention due to the late diagnosis of Syndrome Marfan. Syndrome Marfan usually detected in childhood or adolescence, especially in the presence of bone abnormalities. The presence of funnel chest deformity should have been attract the attention of pediatricians, and subsequently therapists during medical examinations.

Keywords: hereditary disorders of connective tissue, connective tissue dysplasia, malocclusion, dental growth disorders, facial dysmorphia, Marfan syndrome.

Currently, hereditary connective tissue disorders (HCTDs) are rare diseases, the diagnosis of which is carried out according to internationally agreed criteria (Marfan, Ehlers-Danlos, Stickler, Lewis-Dietz syndromes and others), and a number of dysplastic phenotypes (marfanoid appearance, Marfan-like and Ehlers-like phenotypes, benign joint hypermobility). Most NNCTs are characterized by the involvement of the skeletal system in the dysplastic process [1]. Marfan syndrome (SM) is a classic example of a monogenic hereditary connective tissue disorder (MCTD) with an autosomal dominant mode of inheritance, high penetrance and varying degrees of expressivity. The disease is hereditary in 75-80% of cases, but can develop as a result of spontaneous mutations. A connection has been established with mutations in the fibrillin 1 gene (FBN1) on chromosome 15q21.1, the TGFβR1 and TGFβR2 genes on chromosome 9 and 3p24.2-P25, which determines the clinical variability of the disease [2].

Clinical manifestations. SM can occur in the form of clearly expressed (expanded) and erased (abortive) forms. The symptom complex mainly includes the following clinical signs: tall stature, arachnodactyly, skeletal deformities, visual impairment, pathology of the heart and large vessels [10]. In severe cases, the disease can manifest itself in the neonatal period with the development of heart valve insufficiency and dilatation of the proximal aorta, aggravating heart failure, which leads to the death of the child during the first year of life. The erased form is manifested by a predominant lesion of one of the body systems (cardiovascular, visual organs, musculoskeletal system) [3].

Patients with SM have typical clinical manifestations, including a tall and slender build, arachnodactyly, flatfoot with hallux valgus (Fig. 1), mitral valve prolapse, aortic dilatation, and ectopic lentis. Currently, the diagnosis of SM is based on identifying two “big” signs of this disease - aortic enlargement and ectopic lens [6,7]. In the absence of “major” signs, hereditary history and molecular genetic data (confirmed fibrillin-1 mutation) are taken into account. All external and visceral signs specific to SM were assigned diagnostic scores (from 1 to 3); with a score of 7 or more points, one should speak of systemic involvement of connective tissue, which is also taken into account as an

independent sign of SM [4,5].

The diagnostic algorithm for SM includes facial dysmorphia, which includes dolichocephaly (long and narrow head shape), enophthalmos (deep position of the eyeballs), slanted down palpebral fissures, hypoplasia of the zygomatic bones, as well as retrognathia (displacement of the lower jaw in the dorsal direction - backwards) [9]. The specificity of these signs is low - the Ghent criteria for SM indicate that identifying at least three of the listed facial dysmorphias adds only one point for systemic involvement of connective tissue; the detection of one or two dysmorphies does not at all affect the diagnosis of SM. Such a sign as an arched palate, given in the first edition of the Ghent criteria (1996), is absent in the revision of the 2010 recommendations (Table 1), due to low specificity in identifying SM [11].

With SM, adentia is often recorded (Fig. 2), the roots of the teeth are usually longer, elongated and pointed, and cleft palates and uvula of the soft palate are less often found. Facial dysmorphias in such patients include a high and wide palate, retrognathia, atrophy of the lower jaw with a pronounced lack of space in it for teeth and, as a consequence, severe malocclusion and crowding of teeth. In addition, dysfunction of the temporomandibular joint and its subluxations are often detected. Disocclusion leads to uneven load on individual teeth, which leads to their loosening, abrasion, as well as gingivitis and, ultimately, multiple caries [8].

The diagnosis of Marfan syndrome requires, at a minimum, the presence of one major criterion in two systems and the involvement of a third system in the pathological process.

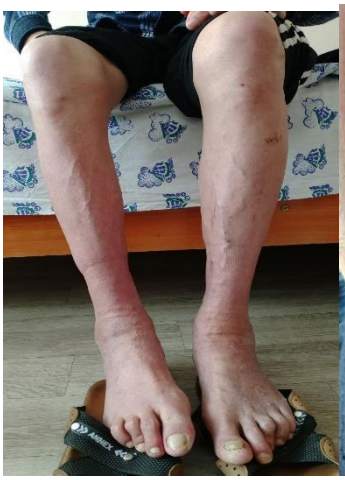
1-table

Scoring of signs of systemic involvement of connective tissue according to the Ghent criteria (2010).

Signs	score
Wrist and thumb symptom	3
Wrist or thumb symptom	1
Pileated chest deformity	2
Pectus excavatum or asymmetry of the chest	1
Hallux valgus	2
Flat feet	1
Pneumothorax	2
Ectasia of the dura mater	2
Protrusion of the hip joint	2
Reduced upper to lower body segment ratio and increased arm span to height ratio and mild scoliosis	1
Scoliosis or thoracolumbar kyphosis	1
Underextension of the elbow joint	1
Facial signs (3 of 5): dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia	1

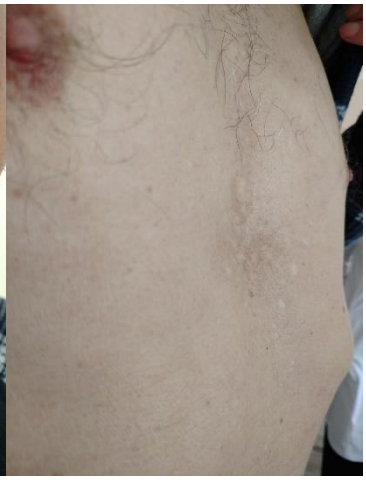
Skin stretch marks	1
Myopia more than 3 diopters	1
Mitral valve prolapse	1

Clinical case. Patient K., DOB 1961, was admitted to the rheumatology department of the multidisciplinary clinic of the Tashkent Medical Academy (TMA) on November 21, 2023 with complaints of pain in the small joints of the arms and legs, morning stiffness, pain in the shoulder, radial and knee joints on both sides, palpitations, shortness of breath with minor physical activity and at night, swelling of the lower extremities. He considers himself sick since the age of 26, but cannot indicate the cause of the disease. In 1987, he was admitted to the hospital at his place of residence with a diagnosis of hemorrhagic stroke with right-sided hemiparesis. After the course of treatment, the patient's condition improved, but limited movements in the right arm and leg (hemiparesis) remained. Subsequently, he was registered with a neurologist and regularly received outpatient treatment. The condition worsened over the course of 4 months before hospitalization, when, for no apparent reason, shortness of breath during physical activity began to be bothered, which had an increasing character, palpitations, severe pain in the joints, morning stiffness, after which the patient turned to a rheumatologist. A diagnosis of rheumatoid arthritis was made and treatment was recommended (prednisolone 10 mg per day, metarthritis 10 mg/week subcutaneously, folic acid). Despite the therapy, his health did not improve, and therefore the patient was hospitalized in the rheumatology department of the TMA multidisciplinary clinic. From the life history: previous diseases: ARVI. Family history: the patient's father and daughter have funnel chest deformity. Results of physical examination: condition of moderate severity, swelling of the feet, legs, hands. Height 186 cm, weight 80 kg, BMI 23.1. Funnel chest deformity (Fig. 3). Auscultation of the lungs: vesicular breathing. Respiration rate 20 per minute.



1-figure. Valgus foot deformity. Flat feet.

2-figure. Adentia



3-figure Funnel chest deformity.

Apex impulse – 1.5 cm outward from the left midclavicular lines in the 5th intercostal space. Heart sounds are muffled, arrhythmic like extrasystole, heart rate is 92 per minute. Systole-diastolic murmur in the 2nd intercostal space on the left.

Results of laboratory research methods: complete blood count: red blood cells - 4.5 million/µl, hemoglobin - 114 g/l, leukocytes - 7.7 thousand/µl, ESR - 21 mm/hour, color index - 0.91, hematocrit - 0.41%, segmented neutrophils – 69%, lymphocytes – 23%, monocytes – 8%. VSC – 2 55 – 3 25. General urine analysis: protein – 0.033 g/l, leukocytes – 13-14 in the field of view, salts-urates +++. Biochemical blood test: total protein – 54 g/l, urea – 9.6 mmol/l, creatinine – 106.1 µmol/l, glucose – 5.5 mmol/l, cholesterol – 3.2 mmol/l, total bilirubin – 16.6 µmol/l, alkaline phosphatase – 119 U/l, AST-60 U/l, AlAT – 90 U/l, potassium – 3.3 mmol/l, chlorides – 97 mmol/l. Acute-phase tests: CRP - 19 mg/l, RF - 22 IU/ml, antistreptolysin - O - 300 IU/ml. Coagulogram: prothrombin time - 25.2 seconds (normally up to 30 seconds), plasma tolerance to heparin - 5-20, fibrinogen - 266 Mr/d, PTI - 16.1 seconds / 56%, INR - 1.29, ethanol test – negative, thrombotest – V degree.

Results of instrumental research methods and consultations with medical specialists. ECG on admission: sinus tachycardia, heart rate – 100 beats per minute. EOS is deviated to the right. P-pulmonale, incomplete block of the right bundle branch, ischemic changes in the myocardium of the posterior and anteroseptal region of the left ventricle. Signs of hypertrophy of both ventricles. Chest X-ray (11/21/2023): X-ray signs of chronic bronchitis. EchoCG (11/21/2023): the left ventricular cavity is not dilated, EDR – 36 mm, EDV – 54 ml, EF – 66%, LA – 2.9 cm. The right parts of the heart are markedly dilated. The thickness of the anterior wall of the pancreas is 1.5 cm. The tricuspid valve is compacted, thickened, with uneven contours. The mitral valve is sealed. The aorta is compacted: the diameter at the level of the aortic valve is 29 mm. Pulmonary artery - age norm: root diameter 27 cm. The walls of the left ventricle are compacted, dyskinesia of the IVS according to the type of paradoxical movement. TMZhP – 0.9 cm, TZSLZh – 1.0 cm. Doppler EchoCG: Tricuspid regurgitation of 2-3 degrees. Conclusion: Tricuspid valve insufficiency of the 3rd degree. Overload of the right departments. Pulmonary hypertension 1-2 degrees. Global contractility of the LV myocardium is normal.

Ultrasound of the thyroid gland with superficial lymph nodes (11.21.2023): without echo pathology. Ultrasound of the abdominal cavity and kidneys: diffuse changes in the liver. Cholelithiasis.

Based on complaints, anamnesis, objective data and the results of laboratory and instrumental studies, the patient was diagnosed with Marfan syndrome: skeletopathy, damage to the heart (tricuspid insufficiency of the 3rd degree), the central nervous system (a condition after a hemorrhagic stroke with hemiparesis). Complication: Chronic heart failure stage IIB (NYHA FC III): pulmonary hypertension, hydropericardium, hydrothorax.

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Conclusion. The presented clinical case deserves attention due to the late diagnosis of SM. SM is usually detected in childhood or adolescence, especially in the presence of bone abnormalities. The presence of funnel chest deformity should have been attract the attention of pediatricians, and subsequently therapists during medical examinations. The existing difficulties in diagnosis are explained by the absence of all typical phenotypic manifestations of SM. A comprehensive examination aimed at searching for changes characteristic of SM and NNTS is indicated for first-degree relatives with the purpose of early diagnosis and correction of possible anomalies.

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