PCSEE
ISSN: 0258-8013
Volume 45, Issue 07, August, 2025

LATE DIAGNOSIS OF MARFAN SYNDROME IN PRACTICE OF RHEUMATOLOGIST CLINICAL CASE

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

DOI:
07.2204/Pcsee.22.10.2025.01

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. Clinical laboratory-instrumental examination of patients diagnosed with Marfan syndrome. 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. 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.

1. INTRODUCTION

Currently, hereditary connective tissue disorders (HCTD) 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 HCTD are characterized by the involvement of the skeletal system in the dysplastic process [1]. Marfan syndrome (MS) is a classic example of a monogenic hereditary connective tissue disorder (HCTD) with an autosomal dominant type of inheritance, high penetrance and varying degrees of expressivity. The disease is hereditary in 75-80% of cases, but can develop due to spontaneous mutations. A link 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 causes 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 dilation of the proximal aorta, aggravating heart failure, which leads to the death of the child during the first year of life. The latent form is manifested by predominant damage to one of the body's systems (cardiovascular, visual organs, musculoskeletal system) [3].

Patients with SM have typical clinical manifestations, including tall and slender build, arachnodactyly, flat feet with hallux valgus (Fig. 1), mitral valve prolapse, aortic dilation, and ectopia lentis. Currently, the diagnosis of SM is based on the identification of two “major” signs of this disease - aortic dilation and ectopia lentis [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 are assigned diagnostic points (from 1 to 3); when a score of 7 or more points is collected, one should talk about 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 include dolichocephaly (long and narrow head shape), enophthalmos (deep position of the eyeballs), downward-slanting palpebral slits, hypoplasia of the zygomatic bones, and retrognathia (dorsal displacement of the lower jaw - backward) [9]. The specificity of these signs is low - the Ghent criteria for SM indicate that the detection of at least three of the listed facial dysmorphias adds only one point for systemic involvement of connective tissue, the detection of one or two dysmorphias does not affect the diagnosis of SM at all. Such a sign as an arched palate, given in the first edition of the Ghent criteria (1996), is absent from the 2010 revision of the recommendations (Table 1), due to low specificity in identifying SM [11]. In SM, adentia is often recorded (Fig. 2), the roots of the teeth are usually longer, elongated and pointed, clefts of the palate and uvula of the soft palate are less common. Facial dysmorphia in such patients include a high and wide palate, retrognathia, atrophy of the lower jaw with a pronounced deficit of space in it for teeth and, as a result, severe bite disorders and crowding of teeth. In addition, dysfunction of the temporomandibular joint and its subluxations are often detected. Dysocclusion leads to uneven loading on individual teeth, which leads to their loosening, abrasion, as well as gingivitis and, ultimately, multiple caries [8].

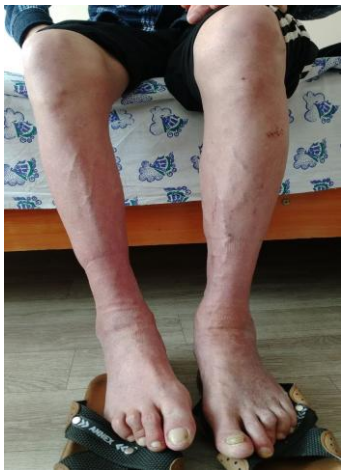
The diagnosis of Marfan syndrome requires, at a minimum, the presence of one major criterion in two systems and the involvement of a third system in the pathological process.

Table 1 Scoring of signs of systemic involvement of connective tissue according to the Ghent criteria (2010).

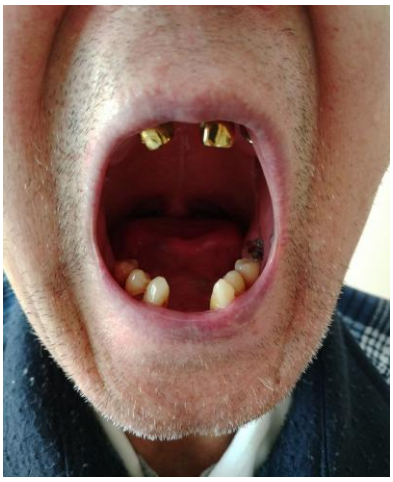
Signs	Points
Wrist and thumb sign	3
Wrist or thumb sign	1
Pectus carinatum	2
Pectus excavatum or chest asymmetry	1
Horses valgus	2
Flat feet	1

Pneumothorax	2
Dura mater ectasia	2
Hip protrusion	2
Decreased upper to lower body ratio and increased arm span to height ratio and mild scoliosis	1
Scoliosis or thoracolumbar kyphosis	1
Elbow underextension	1
Facial signs (3 of 5): dolichocephaly, enophthalmos, downward slanting palpebral fissures, hypoplasia of the zygomatic bones, retrognathia	1
Skin striae	1
Myopia greater than 3 diopters	1
Mitral valve prolapse	1

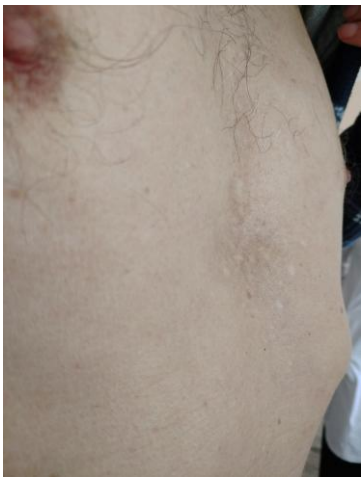
Clinical case. Patient K., born in 1961, was admitted to the rheumatology department of the multidisciplinary clinic of the Tashkent Medical Academy (TMA) on November 21, 2023, complaining of pain in the small joints of the arms and legs, morning stiffness, pain in the shoulder, radius and knee joints on both sides, palpitations, shortness of breath with minor physical exertion and at night, swelling of the lower extremities. Considers himself ill since the age of 26, 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 movement in the right arm and leg (hemiparesis) remained. Subsequently, he was registered with a neurologist and regularly received outpatient treatment. Worsening of the condition over the last 4 months before hospitalization, when shortness of breath during physical exertion of an increasing nature, palpitations, severe joint pain, morning stiffness began to bother the patient for no apparent reason, after which the patient consulted a rheumatologist. Rheumatoid arthritis was diagnosed and treatment was recommended (prednisolone 10 mg per day, metarthritis 10 mg / week subcutaneously, folic acid). Despite the therapy, the patient's health did not improve, and therefore he was hospitalized in the rheumatology department of the multidisciplinary clinic of TMA. From the anamnesis of life: previous diseases: acute respiratory viral infection. Family history: the patient's father and daughter have funnel chest deformity. Results of physical examination: moderate condition, swelling of the feet, shins, hands. Height 186 cm, weight 80 kg, BMI 23.1. Funnel chest deformity (Fig. 3). Auscultation of the lungs: vesicular breathing. Respiratory rate 20 per minute.



1-picture. Hallux valgus..



2-picture. Adentia.



3-picture. Funnel chest. Flat feet

Apical impulse - 1.5 cm outward from the left midclavicular line in the 5th intercostal space. Heart sounds are muffled, arrhythmic like extrasystole, heart rate is 92 per minute. Accent of the 2nd tone over the pulmonary artery, systolic murmur at the 4th listening point (over the xiphoid process).

Results of laboratory tests: complete blood count: erythrocytes - 4.5 million/μl, hemoglobin - 114 g/l, leukocytes - 7.7 thousand/μl, ESR - 21 mm/hour, color index - 0.9, hematocrit - 0.41%, segmented neutrophils - 69%, lymphocytes - 23%, monocytes - 8%. Urinalysis – 2 55 – 3 25. General urine analysis: protein – 0.033 g/l, leukocytes – 13-14 in the field of vision, urate salts +++. Blood biochemistry: 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, ALT – 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 sec.), plasma tolerance to heparin - 5-20, fibrinogen - 266 Mr / d, PTI - 16.1 sec / 56%, INR - 1.29, ethanol test - negative, thrombotest - grade V.

Results of instrumental research methods and consultations with medical specialists. ECG on admission: sinus tachycardia, HR - 100 beats per minute. EOS is deviated to the right. P-pulmonale, incomplete right bundle branch block, ischemic changes in the myocardium of the posterior and anterior septal 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, EDD - 36 mm, EDV - 54 ml, EF - 66%, LA - 2.9 cm. The right chambers of the heart are significantly dilated. The thickness of the anterior wall of the RV is 1.5 cm. The tricuspid valve is compacted, thickened, with uneven contours. The mitral valve is compacted. The aorta is compacted: the diameter at the level of the aorta is 29 mm. Pulmonary artery - age norm: root diameter 27 cm. The walls of the left ventricle are compacted, dyskinesia of the interventricular septum according to the paradoxical movement type. IVS - 0.9 cm, TZLV - 1.0 cm. Doppler EchoCG: Tricuspid regurgitation grade 2-3. Conclusion: Tricuspid valve insufficiency grade 3. Overload of the right sections. Pulmonary hypertension grade 1-2. Global contractility of the LV myocardium is normal.
Thyroid ultrasound with superficial lymph nodes (11/21/2023): without echo-pathology. Ultrasound of the abdominal organs and kidneys: diffuse changes in the liver. Gallstone disease.

Based on complaints, anamnesis, objective data and results of laboratory and instrumental studies, the patient was diagnosed with: Marfan syndrome: skeletal disease, heart damage (grade 3 tricuspid insufficiency), central nervous system (condition after hemorrhagic stroke with hemiparesis). Complication: Chronic heart failure grade IIB (NYHA III FC): pulmonary hypertension, hydropericardium, hydrothorax. The patient was hospitalized from 11/21/2023 to 11/24/2023. Received the following therapy: piracetam 20% - 10 ml intravenously by jet stream, potassium chloride 4% - 10.0 intravenously by drip, diclofenac 75 mg 3.0 intramuscularly, ascorbic acid 5% - 6.0 intravenously by jet stream, neoton 1.0 g intravenously by drip, heparin 5000 U 4 times a day subcutaneously, ceftriaxone 1.0 g 2 times a day intramuscularly, prednisolone 5 mg 2 tablets/day, veroshpiron 50 mg 1 drop/day. After the course of therapy, the condition improved somewhat. The patient was referred to the Republican Cardiology Center for further treatment and observation.

2. Conclusion

1. The presented clinical case deserves attention due to the late diagnosis of SM. Usually SM is detected in childhood
or adolescence, especially in the presence of bone anomalies. The presence of funnel chest deformity should have attracted the attention of pediatricians, and subsequently therapists during medical examinations.
2. The existing difficulties in diagnosis are explained by the absence of all typical phenotypic manifestations of SM.
3. A comprehensive examination aimed at finding changes characteristic of SM and HCTD is indicated for first-line relatives for the purpose of early diagnosis and correction of possible anomalies.

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