CLINICAL DIAGNOSTIC FEATURES OF MARFAN SYNDROME IN ADOLESCENTS

Makhzuna Mukhsinova
Doctor of Sciences, Associate Professor, Tashkent State Medical University
Tashkent, Uzbekistan
mukhsinovamakhzuna@gmail.com

Abstract. *A case of clinical observation of a patient with connective tissue dysplasia, and specifically with Marfan's syndrome, is presented. This pathology, being a consequence of a number of genetic disorders, includes a group of various systemic conditions. The issues of etiology, clinic and diagnostics of connective tissue dysplasia are covered. The clinical observation of this case is of interest to practicing pediatricians and cardio-rheumatologists.*

Key words: *children, Marfan's syndrome, treatment*.

Hereditary connective tissue disorders and connective tissue dysplasia of a polygenic multifactorial nature are quite common in the population. However, despite the high level of modern molecular technologies, clarification of the nosological form of hereditary connective tissue disorders today still remains a distant prospect. These difficulties are due to the large variety of mutations, the pronounced clinical polymorphism of their phenotypic manifestations, the significant size of the genes encoding numerous connective tissue proteins, the rarity of major mutations, and the low suitability of classical molecular genetic research methods for verifying the diagnosis.[1,2,5,7] Clarification of the incidence of connective tissue dysplasia is hampered by the lack of a unified terminology, unified diagnostic criteria and selection of the same type of groups of patients, as well as the practical inaccessibility of modern molecular genetic methods to identify a genetic predisposition to this heterogeneous pathology. In the last decade, interest in the connective tissue dysplasia problem has increased dramatically. Connective tissue dysplasia is a group of genetically determined diseases caused by defects in fibrous structures and the basic substance of connective tissue and leading to impaired organ and system shaping. Patients with connective tissue dysplasia have an increased risk of sudden death, primarily due to pathological changes in the cardiovascular system (rupture of the aorta, rupture of cerebral aneurysm, acute heart failure due to heart rhythm disturbances and other causes, etc.) [3, 4]. Considering the wide prevalence of connective tissue dysplasia among the population (1 case per 5–47 people) and the frequent damage to the cardiovascular system, early detection of this pathology is an urgent and socially significant task in terms of preventing sudden death of people with signs of connective tissue dysplasia [1]. Depending on the etiological factor, connective tissue dysplasia is divided into differentiated, which include hereditary connective tissue disorders hereditary connective tissue disorders (monogenic connective tissue dysplasia), such as Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, etc., undifferentiated (polygenic) connective tissue dysplasia.

The attention of researchers is directed to studying the problem of the modifying effect of this pathology on the nature of the course of almost all diseases [6,8,13,14]. This justifies the expediency of making additions to the standards of examination and management of these patients with the mandatory inclusion in the complex therapy of the underlying disease of additional therapeutic and rehabilitation measures that correct disorders caused by concomitant pathology. Knowledge of the basic principles of diagnosis and treatment of hereditary connective tissue disorders and connective tissue dysplasia is necessary for doctors of all specialties today. This article is based on modern international experience, as well as the principle of continuity in the interpretation of this pathology by domestic cardiologists and therapists. Our goal is to help the doctor understand the issues of terminology, classification, diagnostic features in children with Marfan syndrome, which has agreed international criteria for detection, as well as unify approaches to diagnosis. [9,10]This will make it possible to compare the results obtained by different researchers, and the presented algorithms for clinical diagnostics, in combination with modern methods of molecular genetic research, can give practically important results in relation to the identification of causative genes.

Clinical example of a patient with a mild form of Marfan 's syndrome .

Patient B., aged 18, was admitted to the hospital with complaints of periodically pressing pains in the region of the heart, shortness of breath when walking, palpitations, headaches, dizziness, increased anxiety, poor sleep, decreased visual acuity and hearing, and periodic pain in the spine.

From the anamnesis it is known that the child is from the 2nd pregnancy, which proceeded against the background of anemia of the 2nd degree and ARI in the 2nd trimester. Birth on time. Up to a year, rickets and anemia were noted. Up to 3 years - frequent colds. Vaccinations received according to the calendar. Heredity - the father has a Marfan-like lesion of the connective tissue, and his uncle has Marfan syndrome.

In the anamnesis since childhood, hearing loss in both ears and vision was noted. Sensorineural hearing loss and progressive keratoconus in both eyes were diagnosed. At the age of 15, within 1 year, he grew by 11 cm, pain in the region of the heart of a pressing nature, shortness of breath and palpitations during physical exertion began to bother. Marfan's syndrome was diagnosed. Throughout life, increased anxiety, poor sleep, weakness, malaise, "shoemaker's chest", and poorly developed muscular musculature attracted attention. Longitudinal flat feet I degree. Tall 192 cm. Long fingers and toes and their excessive mobility. The ring finger of the hand is larger than the index finger, the 2nd toe is larger than the 1st finger, there is a “ sandal -like gap” between them. High sky. Scoliosis. Mass -growth index 28%. There are symptoms of vegetative-vascular dystonia (low blood pressure, hyperhidrosis of the palms and feet, persistent red dermographism).

On the ECG, sinus tachycardia with a heart rate of 100 per 1 min. Vertical position of the electrical axis of the heart. Shortening of the PQ interval to 0.11 s. Violation of conductivity on the right leg of the bundle of His. Echocardiography: end diastolic size of the left ventricle 4 cm, end systolic size 2.7 cm, ejection fraction 56%, size of the right ventricle 2.2 cm, left atrium 2.1 cm, relatively enlarged right atrium 2.9 cm. Moderately pronounced prolapse of

the anterior leaflets of the mitral valve, regurgitation on the mitral valve of the I degree. Tricuspid valve leaflet prolapse with grade I regurgitation. Fuzzy differentiation of the leaflets of the aortic valve, bicuspid aortic valve. Regurgitation on the pulmonary artery II degree. Aortic root 3 cm (normal 3.7 cm), not changed.

X-ray of the chest organs: focal and infiltrative changes were not detected in the lungs. The roots of the lungs are not expanded, structural. The sinuses of the pleural cavities are free. Aperture with clear and smooth contours. The heart is not enlarged. Radiography of the spine osteochondrosis of the discs of the thoracic vertebrae (4-7).

Ultrasound of the abdominal organs - kidneys of normal shape, size and position. The mobility of the kidneys is excessive up to 5 mm. Ultrasound of the thyroid gland - small cysts of the right lobe of the thyroid gland, in the right lobe in the upper, middle and lower segments there are three hypoechoic formations 2 mm in diameter, creating the effect of distal amplification.

Clinical diagnosis: Marfan 's syndrome with damage to the cardiovascular system: mitral valve prolapse of the 1st degree with moderate regurgitation . Migration of the supraventricular pacemaker, paroxysmal sinus tachycardia. Chronic heart failure I degree. Musculoskeletal disorders: dolichostenomelia, keeled chest, longitudinal flat feet. Nephroptosis on the right II degree. Chronic pyelonephritis, remission. Widespread osteochondrosis of the spine. Biliary dyskinesia of the hypomotor type. Long-term consequences of a brain injury (brain concussion in 2015) in the form of asthenovegetative syndrome and scattered focal symptoms. Small cysts in the right lobe of the thyroid gland. Decreased visual acuity of the right eye to 0.1 D, the left - to 0.04 D due to progressive keratoconus in both eyes. Chronic bilateral hearing loss.

Conducted therapy: β-blockers (anaprilin 40 mg), infusion therapy (Mexidol, Cavinton), vitamin therapy (milgamma). The impact of β-blockers in connective tissue dysplasia is not limited to the elimination of manifestations of vegetative dystonic syndrome. The participation of the sympathetic- adrenal system in collagen formation allows us to consider β-blockers in the context of pathogenetic therapy. In particular, blockade of β-adrenergic receptors in fibroblasts leads to a decrease in the level of cAMP, which directly correlates with the rate of intracellular breakdown of newly synthesized collagen. Thus, treatment with β-blockers makes it possible to control the intensity of intracellular collagen breakdown and thereby increase its production.

The pathogenetic rationale for vitamin therapy is the participation of these substances in the metabolism of connective tissue. The growth of collagen chains and the maturation of its molecules occur under the influence of the enzymes proline and lysyl hydroxylase, the cofactor of which is ascorbic acid. Vitamin C enhances collagen synthesis by stimulating procollagen mRNA .

A beneficial effect on the state of collagen and vitamin B6 is known. Its coenzyme form is related to the deamination of lysine and oxylysine , amino acids that provide the strength of the cross-links of the collagen molecule. Under the influence of vitamin A, thickening of collagen and elastic fibers occurs.

Ions of calcium, magnesium, potassium, sodium are part of the basic substance of the connective tissue and are involved in the regulation of its metabolism. Among the possible pathogenetic mechanisms of connective tissue dysplasia, much attention is paid to the deficiency of magnesium ions. It has been established that under conditions of magnesium deficiency, the ability of fibroblasts to produce collagen is impaired. It is assumed that magnesium deficiency primarily affects the activity of magnesium-dependent adenylate cyclase, which ensures the removal of defective collagen.

Clinical case No. 2: Patient K., 14 years old, was admitted to the pediatric department with a diagnosis: "Rheumatoid arthritis, articular form, subacute course, activity grade 2, physical activity - 0". Concomitant diagnosis: “Undifferentiated connective tissue dysplasia. Baker's cyst on the right.

From the anamnesis it is known that the child is from the 4th pregnancy, which proceeded without features. Birth on time. Up to a year, exudative diathesis and rickets were noted. Up to 5 years old - frequent colds, at 4 years old he suffered from scarlet fever, at 2 - chicken pox. Allergological history - reaction to penicillin, chocolate, citrus fruits. Heredity in the mother marked hypermobility of the joints.

The real disease began at the age of 7 years, when parents accidentally noticed a swelling in the left popliteal region. Was observed by a surgeon with a diagnosis of hygroma. Treatment was not carried out. After 2 months, the swelling disappeared on its own. From the age of 8, he began to play football, and his parents again noticed a cyst in the right popliteal region, which also disappeared on its own after 1 month. At the age of 8, he was treated in the surgical department for arthritis of the left knee joint, where a plaster splint was applied. There was a positive effect. However, after 5 months, swelling and pain of the knee joints reappeared, and therefore, he was hospitalized in the clinic, where he was diagnosed with rheumatoid arthritis, articular form, subacute course. Received aspirin, delagil, cyclophosphamide was administered intraarticularly with hydrocortisone. Discharged with improvement. Six months later, a new exacerbation of the disease arose, and therefore, he was re-treated at the TashPMI clinic , then 1 time was in a sanatorium-and-spa treatment. The process gradually included the ankle and wrist joints.

On admission to the clinic, the general condition of the boy was satisfactory. The skin is clean, dry, of normal color. Signs of DST were noted - increased extensibility and wrinkling of the skin, kyphosis thoracic spine, bilateral longitudinal flat feet, severe hypermobility, joint subluxations, high palate, hallux valgus, a lot of "tissue paper" scars on the legs, an expanded venous network on the chest, malocclusion. Peripheral lymph nodes were palpated: submandibular, inguinal, axillary. Heart sounds are slightly muffled, soft systolic murmur at the apex and physiological accent 2 tones on the pulmonary artery. BP-110/60 mm Hg. Art. Vesicular breathing in the lungs. The abdomen is soft and painless. The liver and spleen are not palpable. The gait has not changed. There is swelling of the dorsal surface of the wrist joints with small bursitis. Both knee joints are enlarged due to the exudative component, there is a cyst in the right popliteal region, the function of the joints is not impaired; both ankle joints were defigured due to the exudative proliferative component of inflammation with

multiple small bursitis. Violated rotation in the right hip joint. In the blood test - hemoglobin - 128 g/l, leukocytes - 6.2x10 ^{9}/l, ESR -4 mm/h. Blood immunoglobulins within the age norm.

Puncture of the left knee joint yielded 25 ml of a light yellow transparent liquid with reduced viscosity. Cytosis, neutrophils - 14%, mononuclear cells - 86%, RF - negative.

Examination of the ophthalmologist - pathology is not revealed. Radiography of the knee joints with cyst contrasting: no bone changes were detected. In the popliteal region on the right there is an oval-shaped cavity - 3x5 cm, evenly filled with a contrast agent. X-ray of the hands and wrist joints: no bone changes were detected. Timing of ossification by age. Periarticular soft tissues are compacted. For diagnostic purposes, arthroscopy of the left knee joint and biopsy of the synovial membrane were performed. The results of the histological conclusion: chronic synovitis with a high degree of activity of the local inflammatory process. The changes do not quite fit into the picture of rheumatoid arthritis, the possibility of reactive synovitis is not ruled out.

Treatment: Ortofen 75 mg per day, intra -articular - hydrocortisone, exercise therapy, massage. When examining the boy in follow -up after 11 years from the onset of the disease, there were no data for rheumatoid arthritis. Visceral pathology was absent. Peripheral lymph nodes are not enlarged. On the part of the joints: moderate hypotrophy of the thigh muscles, a rough crunch when bending in the knee joints. Outwardly, the knee joints are not changed, the function is not impaired, on the right - a popliteal cyst; in the area of the wrist joints - small bursitis. During the last 3 years the boy has not taken any medications. Periodically, swelling of the knee joints appeared, which independently passed. Every year he was treated in a sanatorium.

Thus, on the basis of clinical, laboratory, radiological and histological data, taking into account the long-term follow -up, juvenile chronic arthritis, incomplete clinical and - laboratory remission, FN-0 was diagnosed. Concomitant diagnosis: “Undifferentiated connective tissue dysplasia. Right sided Baker's cyst.

The diagnosis of this patient presented certain difficulties, for the reason that the disease was clearly progressive in nature, involving all new joints, including the joints of the hands. This could indicate the possibility of rheumatoid arthritis. But there were also some features in the clinical picture of the disease that did not allow to confirm this diagnosis definitively. These include the onset of the disease with the formation of a popliteal cyst, which is not quite typical for rheumatoid arthritis, its recurrence after physical exertion, involvement in the process of one hip joint, which is also not typical for this disease. And, finally, the absence of a radiographic picture of the joints typical of a long-term course of rheumatoid arthritis and slight changes in both the immunogram and the composition of the synovial fluid. All this led to doubts about the diagnosis of rheumatoid arthritis and to perform arthroscopy and biopsy of the synovial membrane, which did not confirm this diagnosis. A follow-up examination 11 years after the onset of the disease made it possible to settle on the diagnosis of juvenile chronic arthritis against the background of UCTD.

Thus, connective tissue dysplasia is a systemic pathology, covering almost all organs and systems, with progressive development starting from puberty. This pathology, depending on the degree of severity and organ specificity, is a risk factor for sudden death, primarily in

people of young working age who lead an active lifestyle and consider themselves practically healthy. Timely detection of signs of Marfan syndrome at the clinical level will prevent the development of life-threatening complications and develop a plan for personalized prevention and treatment in order to increase life expectancy.

LITERATURE

1. Bockeria L.A., Revishvili A.Sh., Neminushchiy N.M. //Sudden cardiac death. M.: GEOTAR - Media, 2011; 272p. [Bockeria LA, Revishvili A.Sh ., Neminushchiy N.M. Sudden cardiac death. Moscow: GEOTAR-Media, 2011; 272 pp. (in Russian).]

3. Dolzhansky Oh.V., Shilova M.A., Paltseva E. M. and others. Aortic aneurysm in idiopathic cystic median necrosis Erdheim in pathoanatomical and forensic practice. Archive of pathology. 2016; 4(78): 3–9. [Pigolkin Yu.I ., Dolzhansky OV, Shilova MA, et al. Aortic aneurysm in Erdheim's idiopathic cystic medial necrosis in autopsy and forensic medicine. Archive of pathology. 2016; 4 (78): 3–9 (in Russian).]

4. Duraković Z., Mišigoj Duraković M., Škavić J. Arhythmogenic right ventricular dysplasia and sudden cardiac death in Croatians, young athletes in 25 years. Collegium antropologicum. 2011; 35(3): 793–796.

5. Hereditary disorders of connective tissue. Russian recommendations. M., 2012; 49c. [Hereditary disorders of connective tissue. Russian recommendations. Moscow, 2012; 49 pp. (in Russian)]

6. Kadurina T.I., Gorbunova B. Dysplasia connective fabrics. St. Petersburg: ELBI - St. Petersburg, 2009; 704 p. [Kadurina T.I., Gorbunova V. Dysplasia of connective tissue. St. Petersburg: ELBI- SPb, 2009; 704pp. (In English)].

7. Kogan E.A., Nikolenko B.N., Zanozin A.C. and others. Syndrome of undifferentiated connective tissue dysplasia in combination with hereditary thrombophilia as a cause of primary female infertility. Medical Bulletin of the North Caucasus. 2016; 11(2–2): 323–326. [Kogan E.A., Nikolenko V.N., Zanozin A.S. et al. Syndrome of undiff erentiated connective tissue dysplasia in combination with hereditary thrombophilia as the cause of primary female infertility. Medical news of the North Caucasus. 2016; 11(2–2): 323–326 (in Russian).]

8. Martynov A.I., Nechaeva G.I. National recommendations of the Russian Scientific Medical Society of Physicians for the diagnosis, treatment and rehabilitation of patients with connective tissue dysplasia. Moscow, 2016; 76 p. [Martynov A.I., Nechaeva G.I. National recommendations of the Russian Scientific Medical Society of Physicians for diagnosis, treatment and rehabilitation of patients with dysplasia of connective tissue. Moscow, 2016; 76pp. (in Russian).]

9. Mikhailin E.S., Ivanova E.A., Shilo M.M. Primary diagnosis of Marfan's syndrome in a pregnant woman aged 16 years: a clinical case. // Issues of modern pediatrics. - 2019; T.18. - №2,

10. Мухсинова М.Х. Малые аномалии сердца у детей (обзор литературы). / Мухсинова М.Х., Хужаева Ф. С., Абдувохидов Ж.З. // Re-health journal. -2021. - №2(10). С. 173-181.

11. Muxsinova M.X. Bolalardagi kichik yurak anomaliyalarining klinik va funktsional xususiyatlari./ Muxsinova M.X., Ortikov U.U., Xujaeva F., Abduvohidov J.Z., Abdurazakova Z.K. // Евразийский вестник педиатрии. 2021. - №3(10). - С.98-104.

12. Pigolkin Yu.I., Shilova M.A., Globa I.V. Vascular pathology in the aspect of sudden death of young people and connective tissue dysplasia: anatomical, physiological and morphological parallels. Angiology and vascular surgery. 2017; 1(23): 36–42. [Pigolkin Yu.I., Shilova M.A., Globa I.V. Vascular pathology in the aspect of sudden death among young people and dysplasia of connective tissue: anatomical, physiological and morphological parallels. Angiology and vascular surgery. 2017; 1(23): 36–42 (in Russian).]

13. Pigolkin Yu. I., Shilova M A., Kildyushov E. M., Galchikov Yu. I. Forensic characteristic reasons sudden of death at persons young age. Forensic examination. 2016; 5(59): 4–9. [Pigolkin Yu.I., Shilova MA, Kildyushov E.M., Galchikov Yu.I. Forensic medical characteristics of the causes of sudden death in young people. Forensic and medical examination. 2016, 5 (59): 4–9 (in Russian).]

14. Shilova M.A., Mamedov M.N. Sudden cardiac death in young people: risk factors, causes, morphological equivalents. Cardiology. 2015; 7(55): 78–83. [Shilova M.A., Mamedov M.N. Sudden cardiac death in young people: risk factors, causes, morphological equivalents. Cardiology. 2015; 7 (55): 78–83 (in Russian).]