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MODERN VIEW OF THE PROBLEM OF CONNECTIVE TISSUE DYSPLASIA WITH ANEMIA

(Literature Review)

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Connective tissue occupies a special place in the body in terms of its importance. It makes up approximately 50% of the total body mass and forms the skeleton and outer skin , and also participates in the formation of the internal environment of the body, through which all structural elements receive nutrients and remove metabolic products. Connective tissue during embryogenesis develops from the mesenchyme, from which tissues that are so dissimilar to each other are formed from the outside: skin and bones, blood and lymph, cartilage and smooth muscles, which have not only a common origin, but also a common structure and functions [45, 46,48].

The unique properties of collagen can explain the versatility of connective tissue. Collagen makes up more than 30% of the total body weight in our body and is found not only in the skin and skeletal tissues (40-50%), but also in the stroma of internal organs (10% of their mass). [26].

The development of congenital or hereditary defects of connective tissue can lead to disruptions of vital functions of organs and systems, in the implementation and functioning of which connective tissue takes part [31,45]. Genetic heterogeneity of anomalies in the development of defects and diseases of connective tissue can be explained by its constituent genes, which control a huge number of links in the connective tissue system.

Over the past two decades, the number of studies and publications devoted to the study of connective tissue dysplasia has increased, and this is primarily due to the

increased incidence of this pathology. [28,49,17]

Currently, a large group of monogenic DSTs is known, associated with mutations in genes of extracellular matrix proteins (various types of collagens, tenaskin , fibrillin), genes of growth factor receptors (transforming growth factor -^) and matrix metalloproteinases . [30,31] Genes leading to the development of DST encode the synthesis and development of collagen and its spatial organization, structural proteins and protein-carbohydrate complexes. Mutations of these genes lead to the development of over 250 types of DST (Kadurina T.I., Gorbunova V.N., 2007, Zemtsovsky E.V., 2009). Abnormal collagen synthesis, excessive collagen degradation, disruption of the structure of collagen fibers, similar anomalies, tissue destruction as a result of autoimmune reactions can also cause the development of DST. Numerous proteins, genes, enzymes and coenzymes to them are involved in the formation of full-fledged collagen throughout all of the listed stages. To date, there is no generally accepted classification of DST. [13,14,43] DST can be classified taking into account the genetic defect in the period of synthesis, maturation or breakdown of collagen [54]. In practice, it is customary to divide CTD into differentiated (syndromic) and undifferentiated (non-syndromic) forms. Differentiated (syndromic) dysplasias are usually very rare, but have a distinct clinical picture that is established by genes and biochemical defects, a certain type of inheritance. This type of dysplasia includes well-studied and well-known syndromic forms such as Marfan syndrome , Ehlers-Danlos syndrome , osteogenesis imperfecta, Stickler syndrome, Alport syndrome , etc. [16,19]. The spectrum of clinical symptoms of the disease is determined by quantitative and qualitative disorders of collagen biosynthesis and differentiation. Undifferentiated (non-syndromic) forms of CTD are a genetically heterogeneous group that is caused by primary gene disorders and manifests itself as incomplete, erased, undifferentiated forms of anomalies [14,18,15]. Until now, attempts to define and classify pathology associated with congenital musculoskeletal dysplasia have been undertaken mainly by orthopedists and have been reduced to hereditary systemic skeletal diseases [12]. In the literature, there

is a term "osteodysplasia", which refers to a bone tissue developmental defect caused by the cessation, slowing down or disruption of osteogenesis at a certain stage of embryonic or postnatal development [13]. Locomotor changes in systemic underdevelopment of connective tissue are united under the term "bone dysplasia".

However, from the position of an internist, with this approach, the often severe changes in the internal organs observed in this pathology remain outside the field of observation.

T.I. Kadurina , having based the achievements of molecular genetics in the field of collagen biosynthesis, proposed the term " collagenopathy ". The term " collagenopathy " in its meaning is similar to hereditary CTD, but reflects only genetically determined defects of collagen structures in ontogenesis and organogenesis and does not fully characterize all musculoskeletal dysplasia. However, a clear identification of genetic defects allows us to classify collagenopathies with the identification of conditions caused by gene mutations at the stages of collagen synthesis or breakdown [11]. Using this classification of collagenopathies, we can also identify clinical syndromes of differentiated and undifferentiated dysplasia, the consideration of which is of interest not only to medical geneticists, but also to clinicians. To date, there is no precise data on the prevalence of connective tissue dysplasia. As studies have shown [21, 47], individual phenotypic manifestations of CTD are detected in 20-80% of the population.

The consideration of CTD by individual nosological units is explained by narrow specialization in medicine [35, 41, 18]. A certain contribution to the collection of data on the occurrence of CTD in the population is made by the ambiguity of classification and diagnostic approaches [51]. According to some authors, looking at the presence of three external markers of dysplasia, one should decide on the presence or absence of CTD. Others consider the detection of four external signs for women and five for men to be the threshold of stigmatization (Klemenov AV, 2005). V.A. Tabolin and N.P. Shabalov (2010), E.V. Zemtsovsky (2000) suggest the presence of six or more external signs as the threshold for diagnosing CTD. There is also an opinion that 6-8 signs of dysplasia are necessary for diagnosing CTD (Kadurina TI, Gorbunova VN, 2007). Due to the lack of

specific criteria for the stigmatization threshold, it is difficult to compare the results of studies obtained by different authors. However, most specialists come to the conclusion that diagnosing formally with a quantitative approach will lead to hyperdiagnosis, thus, more importance is attached to the qualitative composition of phenotypic signs of dysmorphogenesis [24,28,31]. Scientists have developed a concept of varying significance of dysmorphogenesis signs , but at the same time, the researchers' ideas about the main and secondary signs of CTD differ significantly [21,24,27].

DST leads to an unfavorable course of pregnancy and childbirth, to a limitation of professional choice, determines unsuitability for military service, high disability, as well as cases of early and sudden death, thereby explaining its important medical and social significance.[19,27]

Due to the diversity of clinical manifestations of CTD, it is difficult to combine many symptoms together. Congenital or hereditary defects of connective tissue can lead to disruption of vital functions of the body, thus having a serious prognosis for the life and vital activity of patients. The polyorganism of lesions in CTD is explained by the comprehensive spread of connective tissue in the body. [15,33,17]

Conditions associated with CTD are classified from a clinical perspective as follows [16]:

I. Systemic hereditary syndromes of CTD:

A. Diseases associated with a defect in the biosynthesis and degradation of collagen: Marfan syndrome , Ehlers-Danlos syndrome , osteogenesis imperfecta, lax skin syndrome, dystrophic bullous epidermolysis .

II. Systemic hereditary diseases of connective tissue with locomotor and locomotor -visceral manifestations.

Locomotor manifestations include:

1. Deformation of the chest (funnel-shaped, keel-shaped).
2. Deformation of the spine (kyphosis, lordosis, scoliosis, “straight” back).
3. Pathology of the muscular system (hypotrophy, muscle hypotonia, diastasis of the rectus

abdominis muscles, ventral hernias).

4. Osteochondral dysplasia (physeal , epiphyseal , metaphyseal , diaphyseal , spondyloepiphyseal).

Visceral manifestations include:

1. Changes in the respiratory system: congenital tracheobronchomegaly , congenital tracheobronchomalacia , Williams-Campbell syndrome, Leschke's bronchiectatic emphysema, pulmonary hypoplasia.
2. Changes in the cardiovascular system: prolapse of heart valves, dilation of the roots of the aorta and pulmonary artery, aneurysms of the vessels of the heart, medium and small caliber vessels, varicose veins.
3. Changes in the nervous system: vegetative-vascular dystonia syndrome, nervous anorexia, hemicrania.
4. Changes in the gastrointestinal tract: dyskinesia of the gallbladder and bile ducts, gastroptosis, megacolon, dolichosigma .
5. Kidney changes: nephroptosis, renal dysplasia.
6. Changes in the organ of vision: myopathy, astigmatism, dislocation and subluxation of the lens, congenital strabismus, deep angle of the anterior chamber of the eye.
7. Pathology of ENT organs: otosclerosis, deviated nasal septum, arched palate.
8. Changes in the skin: thin, translucent, easily damaged skin, excessively dry or hyperelastic skin; easy bruising; skin stretch marks ; tissue-paper-like scar.

In 46.6-72.0% of cases of CTD, magnesium deficiency was detected, which is why researchers admit the pathogenetic significance of hypomagnesemia in the development of CTD. Magnesium ions are the main substance of the connective tissue structure, and with magnesium deficiency, fibroblasts lose the ability to produce collagen. Magnesium deficiency leads to a slowdown in the biosynthesis of structural molecules of connective tissue, characterized by abnormal formation of collagen chains. In this regard, the formation of connective tissue in the form of a chaotic arrangement of collagen fibers is disrupted. [18,23,37] From the standpoint of modern concepts, connective tissue dysplasia (CTD) is considered as a disorder of connective tissue development in the embryonic and

postnatal periods, accompanied by morphofunctional disorders of organs and systems, and a progressive course [3, 9, 20]. As is known, hematopoietic tissue and blood cells embryogenetically originate from the mesenchyme and are a type of connective tissue [87]. At present, the state of the vascular-platelet and coagulation links of the hemostasis system and the erythropoiesis system in CTD has been studied in sufficient detail . Without any doubt, disorders in the hematopoietic system affect the life and work prognosis of patients with CTD and require additional examination and treatment.

Anemia is a clinical and laboratory symptom complex characterized by a decrease in the concentration of hemoglobin in a unit of blood volume and, in the vast majority of cases, the number of erythrocytes. [88,90] Normally, the content of erythrocytes in the peripheral blood in men averages (4.0–5.2) x 1012/l, in women – (3.6–4.7) x 1012/l; the hemoglobin level is 130–160 and 120–140 g/l, respectively. There is the following classification of anemias by severity:

•light: hemoglobin 90-110 g/l;

•average: hemoglobin 70-90 g/l;

•severe: hemoglobin below 70 g/l.

The widespread prevalence of anemia explains the relevance of this problem. According to WHO, about 10% of people in Europe suffer from anemia. This pathology is especially common in old and senile age. According to various researchers, the incidence of anemia reaches up to 61% in men and up to 41% in women. In hospitalized patients, its incidence reaches 36-80%, and in outpatients - 5-14%. [82,94] With an increase in the number of chronic diseases that contribute to the development of anemia with age, its incidence increases. The development of anemia in patients leads to significant deterioration in the quality of life (decreased mental and physical activity, fatigue, depressed mood), aggravates the course of existing pathology and creates a threat of premature death. Using the scanning electron microscopy method, significant changes

were revealed in a group of patients with CTD without the development of anemic syndrome. superficial architecture of red blood cells, characterized by a reduction in the number of discocytes , an increase in the number of transformed and degenerative forms of cells. [34,81,95] The most pronounced disturbances in the morphological picture of red blood cells are registered in people with CTD and anemia syndrome. It has been shown that structural inferiority of erythrocyte membranes is a pathogenetic factor in the development of anemia in people with connective tissue dysplasia . [38]

Quite often, the manifestations of the disease are insignificant, are more cosmetic in nature and do not require special medical correction. In this case, an adequate, dosed regime of physical activity, adherence to the regime of activity and rest, a complete vitamin-rich, protein-rich diet are indicated.

If drug correction is necessary (stimulation of collagen synthesis, bioenergetics of organs and tissues, normalization of glycosaminoglycan levels and mineral metabolism), drugs of the following groups are prescribed:

- vitamin and mineral complexes;
- chondroprotectors;
- mineral metabolism stabilizers;
- amino acid preparations;
- metabolic agents

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