RISK FACTORS THAT CAUSE VARIOUS CONNECTIVE TISSUE DYSPLASIA OF THE SKIN

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Abstract. Hereditary collagenopathies occupy a key place among all connective tissue dysplasias, represented by almost 70 nosologies out of 250. Currently, 29 types of collagen have been identified, 12 of them are involved in skin formation. Thus, collagen proteins in the skin make up almost half of the total mass in the body and of the studied collagens and play a significant role in pathological changes and hereditary diseases caused by various mutations. The incidence of skin lesions in hereditary collagenopathies remains one of the highest and requires special knowledge on this issue from a dermatologist.

Key words: collagenopathies, dysplasias, multi-system pathology, morphologically characterized, normal morphogenesis.

At present, the statement of the famous physiologist A.A. Bogomolets [3] in the 1920s: "The body always has an age of connective tissue, which over the years loses its elasticity, and with it gradually lose flexibility, elasticity, and reduce the amplitude of accommodation all functions of the body."

Connective tissue dysplasia (CTD) is a multi-organ and multi-system pathology with a progressive course, which is based on defects in the synthesis or catabolism of extracellular matrix components or regulators of connective tissue morphogenesis. CTD can be of hereditary monogenic origin (in most cases with an autosomal dominant type of inheritance), but much more often it occurs as a result of various adverse effects on the fetus during its intrauterine development in the presence of a genetic predisposition to impaired embryogenesis. The multi-organ and poly-system nature of the lesion is due to the omnipresence of the connective tissue and approximately the same teratogenic termination period for many human organs and systems - the maximum allowable periods when the impact of an unfavorable factor can cause a violation of normal morphogenesis [8].

CTD is morphologically characterized by changes in collagen, elastic fibrils, glycoproteins, proteoglycans , and fibroblasts, which are based on inherited mutations in genes encoding the synthesis and spatial organization of collagen, structural proteins, and protein–carbohydrate complexes, as well as mutations in the genes of the

corresponding enzymes and cofactors [10]. At the same time, mutations in the genes encoding the synthesis and spatial organization of collagen play a leading role in the development of the clinical picture of CTD [11]. Eight groups of hereditary CTD have been identified, among which hereditary collagenopathies (osteogenesis imperfecta , Chernogubov- Ehlers - Danlos syndrome , bullous epidermolysis , chondrodysplasia , ophthalmopathy , nephropathy, myopathy, anomalies of the joints and the organ of vision) occupy a key place [6] .

Collagens are the main components of the extracellular matrix of most tissues and are included in the protein superfamily [1]. Currently, 29 types of collagen have been identified, denoted by Roman numerals [2]. Collagen isoforms differ in amino acid composition, chromatographic and immunological properties, macromolecular organization, and distribution in tissues [8]. Mature collagen protein molecules are composed of three polypeptide subunits, also called a-chains, forming a structure similar to a trihedral cord. Different types of collagens can be formed by three identical a-chains or by two or three different polypeptides. Thus, there are 40 collagen polypeptide a-chains, each of which is encoded by its own gene [8, 14], 16 such chains were found in the skin (see table **)** . Collagens make up more than 30% of the total mass of proteins in the body, and about 40% is located in the skin [5, 9], which is significantly reflected in a large proportion of skin lesions in various collagenopathies

Of the 29 different types of known collagens, 12 (I, III, IV, V, VI, VII, VIII, XIII, XIV, XV, XVII, XIX) form the skin framework [14], and their defects manifest themselves to varying degrees in most types of CTD.

In the adult dermis, interstitial fibrillar collagen (types I, III, and V) constitutes the largest fraction of collagen, with approximately 80% collagen I and 10% collagen type III (see table **)** . Type I collagen is found in large quantities in the reticular dermis, type III collagen in the papillary layer of the dermis. Collagen type V (pericellular) is detected in the dermis in a small amount (less than 5% of total collagen). It is polymorphic in structure (granules, filaments) and is localized within the papillary layer of the dermis, where it participates in the formation of an exocytoskeleton type framework around vessels, nerves, and skin appendages, on the surface of large collagen fibrils of major type I and III collagens, regulates the lateral maturation of these hair con. Major type IV skin collagen is located inside the dermal -epidermal junction, in the vascular basement membranes, around the vessels and appendages of the epidermis [1, 2, 6, 8, 14, 19].

Short-chain type VI collagen is found throughout the dermis as a component of microfibrillar structures. In interfibrillar spaces, it takes the form of thin, bead-like threads; is able to bind to cells and type I collagen, thus taking part in the spatial organization of many structural components of the extracellular matrix; participates in the regulation of cell migration and differentiation during embryonic development [2,

8]. Epidermal keratinocytes express transmembrane type XVII collagen (180 kD antigen of bullous pemphigus), which is included in the structure of hemidesmosomes — a multiprotein complex a $_6$P $_4$ integrin , plectin and laminin-332 (laminin-5), which mediate the adhesion of epidermal keratinocytes to the basement membrane [8, 15, 17]. The description of type XXIX collagen is not yet complete ; it is assumed that it is mainly contained in the epidermis with an increased level of expression in its suprabasal layers [14] and plays a role in the development of atopic dermatitis [20].

According to T.I. Kadurina [7] and V.I. Gorbunova et al . [4], at present, out of more than 250 nosological forms of pathology in CTD, mutations in the genes of collagen a-chains have been noted in 69 nosologies. The spectrum of diseases caused by mutations in genes encoding proteins with collagen-like domains is quite diverse. Among them, diseases with mutations in skin collagen proteins occupy the leading place: Chernogubov- Ehlers - Danlos syndrome , the classic variants of which are caused by genetic defects in type V collagen; the variety of clinical manifestations of the syndrome is determined by the participation in the genetic control of this condition also of type I and III collagens and enzymes of biosynthesis and catabolism of collagen proteins; epidermolysis bullosa , variants of which are associated with genetic defects in type VII and type XVII collagens. Accompanying symptoms in this kind of pathology are nail dystrophy, imperfect dentinogenesis , periodontal disease. One of the genetic variants of isolated nail dystrophy is caused by mutations in the type VII collagen gene [8].

Thus, skin collagen proteins account for almost half of the total mass of the studied collagens in the human body and play a significant role in pathological changes caused by various gene mutations.

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