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ETIO-PATHOGENETIC ASPECTS AND CLINICAL FEATURES OF LOCAL SIGNS OF CONNECTIVE TISSUE DYSPLASIA MANIFESTED WITH DENTOFACIAL ANOMALIES IN SCHOOL-AGED CHILDREN

The literature review presents the problems of congenital connective tissue disorders, characterized by multifactorial origins, associated with aggressive factors from the external and internal environment, manifesting as various general and local phenotypic traits. Recent studies have demonstrated a direct relationship between anomalies of the dental and jaw system and genetically conditioned factors to some extent. As the child grows, the formation and development of the permanent bite ensure the functional activity of the jaws, the dental system's ligamentous apparatus, the functional activity of the muscles in the jaw and facial area, etc. Anatomical-topographic changes in congenital collagenopathy of the organs and tissues of the oral cavity negatively impact the functional activity of the entire dental and jaw system, indicating their biological interconnection which correlates with each other. According to the results of the conducted studies, the most common dental and jaw anomalies in children and adolescents with dentofacial abnormalities are distal occlusion, narrowing and deformation of the dental-alveolar arches of the upper and lower jaws, and deep incisor overlap. The formation of a permanent bite is a multifaceted complex physiological process, where possible reasons for its disruption are identified by quite a few factors from the external and internal environment, including congenital disorders of connective tissue differentiation. In children during the active growth period and ossification of the facial skeleton bones, a correlation of the negative influence of various risk factors on the growth of the middle zone facial bones is determined, which in the future may contribute to the development of dental and jaw anomalies and deformations. As of today, the prevalence of dental and jaw anomalies does not show a tendency to decrease, and their combination with DSD in children and adolescents is insufficiently studied, which requires further research aimed at early detection of local phenotypic signs and improvement of socio-medical rehabilitation with an interdisciplinary approach.

Keywords: osteogenesis, connective tissue dysplasia, phenotypic manifestations, orphan diseases, joint hypermobility, skin hyperextensibility, gothic palate, dentofacial anomalies, temporomandibular joint dysfunction, dentinogenesis imperfecta and amelogenesis.

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Clinical and epidemiological characteristics of connective tissue dysplasia in children and adolescents. To date, connective tissue dysplasia (CTD) is a common systemic pathology that has a wide range of local and general manifestations, which in some cases can lead to disability in working-age individuals [1, 15]. Meanwhile, the problems of congenital disorders of connective tissue differentiation are not fully understood, which presents certain difficulties in organizing and conducting therapeutic, preventive, and rehabilitation measures [23]. In this regard, further study of genetically determined connective tissue disorders is extremely important for maintaining and strengthening the health of the population, as well as having practical significance for healthcare [1, 3].

The aim of the presented literature review is to analyze data from scientific literature on the etiopathogenetic aspects and clinical features of local signs of connective tissue dysplasia, manifested with dental and jaw anomalies in school-age children.

In the structure of manifestations of EDS in the musculoskeletal system, joint hypermobility is most commonly observed, including the development of pathological processes in the temporomandibular joint (TMJ). In clinical practice, joint hypermobility is more frequently diagnosed in girls, reaching up to 65% prevalence among all age groups of schoolchildren, and up to 6% among adults. According to literature sources, the prevalence of joint hypermobility in EDS among the Asian ethnic population ranges from 15 to 25%, while in the European population it reaches digital levels of 10% [6, 37]. Currently, there is a lack of unified diagnostic criteria and approaches to treatment and preventive measures for joint hypermobility in children and adolescents with congenital dysgenesis in clinical practice [30, 36]. The benign course of joint hypermobility is characterized by excessive mobility in more than four joints without pain symp-

toms, where its severe form is additionally manifested by arthralgia, which in most cases is associated with the presence of joint dislocations and subluxations. In some clinical cases of joint hypermobility in children, complaints may be absent despite the presence of pathological joint mobility, which may be perceived by doctors of various specialties as age-related and constitutional features. Overall, joint hypermobility in joint hypermobility syndrome (JHS) is formed as a result of metabolic process disorders and endocrine pathologies. In this regard, school-aged children with clinical signs and symptoms of hypermobility of the joints is prone to the development of inflammatory-degenerative anatomical-morphological changes in joint tissues, which may become the main pathogenetic mechanism for the formation of spinal deformities and flat feet [16, 40].

It should be noted that connective tissue participates in the formation of the anatomical shape and morphological structure of cardiac tissue, where the influence of various aggressive risk factors leads to the development of pathological processes affecting the cardiovascular system, including insufficiency of heart valves and septa, as well as arteries and veins [26, 35]. Research has established a high prevalence of "dysplastic heart" in undifferentiated connective tissue dysplasia (uCTD), with a prevalence rate of 80%, where minor developmental anomalies (MDA) of the heart in the form of mitral valve prolapse in children in their first year of life are found in 6%, and by ages 6-14, this figure reaches 21-30%, whereas during adolescence, it decreases to 15% [8]. Congenital connective tissue alteration of the valve leaflets leads to the formation of their functional inadequacy and disruption of the autonomic innervation of heart tissue, where a high probability of arrhythmia development arises. A number of authors characterize the presence of a direct relationship between magnesium deficiency and the appearance of defective collagen, which contributes to the development of infectious endocarditis, associated with thromboembolism of large vessels, leading to a fatal outcome [8, 21].

It should be noted that currently there is insufficient information in the literature regarding the frequency of dental and jaw anomalies depending on the severity of dysplastic syndromes (DTS). On average, among individuals with congenital collagenopathies, the prevalence of dental and jaw anomalies and deformities is 33%, while in children and adolescents without signs of DTS, this indicator is three times lower. The most commonly observed issue is deep bite, followed by distal, crossbite, and mesial. Meanwhile, a number of authors assert that the most frequently identified anomalies in the structure of dental and jaw anomalies are distal and deep incisal disocclusion [13, 18]. According to studies conducted, the peculiarity of the manifestations of local phenotypic traits related to dental and jaw anomalies is their wide variation from 12% to 93%, which underscores the relevance of their study in order to improve medical care.

It is important to note that the formation of a permanent bite goes through a number of complex stages, and under the influence of many external and internal factors, disturbances in the formation of occlusion may develop. From the first month of embryonic development, the development and formation of the organs and tissues of the oral cavity begins. In this regard, the negative influence of aggressive factors can alter the genetic program of the fetus, which creates the prerequisites for the formation of dental and jaw anomalies and deformations. After the birth of the child, the physiological process of active growth of the bones of the facial skeleton and the formation of the dental-jaw system begins [17, 24]. Thus, the bone tissue of the nasal septum during the period of active growth contributes to the formation of the sutures of the skull until the complete ossification of the vomer and ethmoid bone. Meanwhile, premature mineralization of the sutures of the cranial bones contributes to the appearance of a curvature of the nasal septum, which directly affects the formation of the maxillary complex. In addition, disturbances in the final ossification of the cranial bones negatively impact the formation of the bones in the middle zone of the face, which may be the primary cause of the development of dysocclusions [19].

It should be noted that according to the conducted research, the data on the prevalence of congenital collagenopathy is ambiguous, which is related to the presence of heterogeneous methodological and technological approaches, as well as various classifications [27, 30]. At the same time, the structure of existing DST classifications is organized by general and local phenotypic signs that determine various symptoms and syndromes interpreted by a scoring system [22]. Based on the severity of DST, the total score obtained is determined depending on the identified phenotypic and visceral signs during the research, which define congenital connective tissue differentiation disorders of mild, moderate, and severe severity [27, 34]. Meanwhile, differentiated forms of EDS include Marfan syndrome and Ehlers-Danlos syndrome, familial traits of hereditary mitral valve prolapse, joint hypermobility, osteogenesis imperfecta, imperfect amelogenesis, dentinogenesis, etc. [2, 37]. According to studies, other hereditary syndromes associated with EDS are identified less frequently than the aforementioned orphan diseases [36]. In modern clinical protocols, undifferentiated EDS is characterized as pathological processes with polygenic origins, having a wide range of common and local phenotypic patterns [9]. The severity of EDS manifestations and the nature of their clinical course to some extent depend on the influence of external factors [2, 42].

At the same time, studies conducted by some authors have shown that dental and jaw anomalies have a hereditary nature, while other researchers believe that genetic predisposition phenotypically manifests under 'favorable' conditions influenced by aggressive external and internal environmental factors [14]. Information indicates that disturbances in bite, leading to subsequent formation of dental and jaw anomalies, are significantly influenced by changes in the jaw bones, periodontal ligament tissues, the temporomandibular joint, chewing and facial muscle groups, etc., which negatively affect the functional state of the dental-jaw system, leading to the formation of malocclusions [17]. Meanwhile, a certain feature of dental anomalies and deformities is their predisposition. Congenital anomalies and deformities of teeth are formed in various genetic diseases, including Down syndrome and Ehlers-Danlos syndrome, protruding ears, skin hyperelasticity, and others. In this case, anomalies in the development of teeth are most commonly identified in congenital dysgenesis, which is related to the histological structure of teeth, composed of connective tissue [13, 36].

It should be noted that the clinical features of the manifestations of EDS lead to certain difficulties in their detection and diagnosis verification, which require a wide range of additional research methods and the involvement of related medical specialists for an objective assessment of the extent of organ and tissue involvement. At the same time, initial manifestations of phenotypic signs of EDS can be identified even during the embryonic period of fetal development, where timely implementation of comprehensive preventive measures can minimize the consequences of congenital collagenop-

athy. Other signs, however, progressively manifest clinically as children and adolescents grow and develop, where the severity of EDS can be exacerbated by various aggressive factors in the external and internal environment as they age. Meanwhile, the formation of symptoms and syndromes of congenital collagenopathy minimally manifests during the neonatal period, where some of the earliest manifestations at 20 weeks of gestation are congenital changes in the left ventricle of the heart and the respiratory system. In school age, anomalies of the heart valves and thoraco-diaphragmatic syndromes develop with the appearance of signs of dysplastic changes in the skeletal system and visual organs [2, 8].

Disocclusions occupy one of the leading places in the structure of diseases of the organs and tissues of the oral cavity, with a prevalence that reaches up to 80% [7, 9, 33]. Dentofacial anomalies and deformations manifest as isolated pathological processes, as well as one of the symptoms of genetic diseases. Studies conducted have established a systematic manifestation that reflects the aggressive course of dentofacial anomalies, where deep incisal overlap is found in 52% of cases, crossbite in 15.3%, and normal bite in 8% among examined age groups of schoolchildren. Meanwhile, anomalies in the position of the teeth are identified in 49.3% of those examined, while canine dystopia is found in 32.66% and incisor dystopia in 16.66%. Additionally, among minor genetically predisposed stigmas of dentofacial anomalies, the most frequently diagnosed is a high palate at 20.66%, as well as changes in the sizes and shapes of teeth, including shovel-shaped teeth at 12.66%, micrognathia at 6%, diastemas at 24.66%, and interdental spaces at 6% [18, 23].

Etiological and pathogenetic characteristics of congenital collagenopathies in children and adolescents. It is important to note that congenital collagenopathies contribute to disturbances in the formation of collagen fiber structure, which can lead to morphological changes in the structural components of cartilage tissue, ultimately resulting in pronounced alterations in the maturation of the epiphyseal growth zone. This can lead to the elongation of long bones, manifesting as pathologies of the musculoskeletal system, caused by damage to the formed connective tissue, leading to the development of dolichostenomelia, arachnodactyly, scoliosis, and flatfoot [4].

It should be noted that the metabolism of bone tissue in children and adolescents with DCT is characterized by a disturbance in the balance of connective tissue synthesis and its resorption [2]. Meanwhile, until the age of 3, a child's musculoskeletal system experiences active growth physiologically, then until puberty, the increase in bone mass slows down [8, 39]. At the same time, a significant portion of the adult population is found to have osteoporosis, where the primary pathogenic mechanism is associated with insufficient accumulation of mineral components during the active growth period in adolescents, which is the main cause of developing osteoporosis with age. In Russia, the total number of people affected is about 14 million, and around 20 million have pronounced signs of osteopenia, which are related to significant disturbances in mineral metabolism that develop during childhood [4, 7]. The frequency of detecting osteopenia among younger and middle school students reaches 32%, while among adolescents it is 57%, with 10% having a history of bone fractures from minor injuries. The presence of the above clinical signs of DCT accounts for a high likelihood of developing osteopenia and osteoporosis in children and adolescents. It has been found that in adolescence, if the level of bone mass decreases from the norm by 5-10%, the likelihood of hip fracture increases by 25-50% in later ages. The above indicates the medical and social significance of the problem of osteoporosis, where further research on bone remodeling processes in adolescents with DCT is a relevant task, including for the prevention of dentofacial anomalies [11].

It should be noted that genetically determined connective tissue disorders are associated with various comorbid conditions of different organs and systems [22]. At the same time, some pathogenetic mechanisms of the development of systemic diseases in schoolchildren with joint hypermobility remain unexplored, which is why in some cases the diagnosis is made by specialists in adulthood [28]. In the development of congenital collagenopathies, genetic predisposition has a direct influence. Thus, in the pathogenesis of joint hypermobility syndrome, specific roles are attributed to the alleles of the s gene of collagen COL1A1, which belongs to the 'null' GST M1 genotype, 'slow' NAT2, and 'fast' 4G/4G PAI1 gene. Meanwhile, the high prevalence of the 'null' detoxification system GST T1 genotype indicates a predisposition to the formation of joint hypermobility. Additionally, the Tt genotype of the VDR gene with a Marfan-like phenotype is more frequently identified, where established osteopenia in the lumbar spine of schoolchildren is associated with the presence of this genotype SS gene COL1A1 [25, 27].

To date, a high prevalence of undifferentiated connective tissue dysplasia (CTD) has been defined in the population of children [20]. In this context, congenital collagenopathy constitutes the morphological basis of multiple organ dysfunctions in children and adolescents, as the majority of organs and systems are genetically composed of connective tissue [11]. Numerous studies have demonstrated the main causal factors in the formation and development of CTD, which include genetically determined changes that lead to disturbances in the synthesis and formation of collagen structures with dysfunctions in protein-carbohydrate metabolism, genetically modified defects in enzymatic activity and their cofactors, resulting in changes in the structure of collagen fibrils, proteoglycans, glycoproteins, and fibroblasts of connective tissue [3, 5].

In the structure of congenital connective tissue differentiation disorders, syndromes and symptoms with symptom complexes associated with genetic mutations in the locus of a specific gene are identified. Thus, the syndrome of dysplasia of the hard tissues of dentin and enamel with osteosclerosis is classified as an autosomal dominant disease. There are numerous gene mutations (currently around 500 are known) that lead to disruptions in the coding of the protein matrix of connective tissue. Furthermore, there is evidence that polygenic forms of genetic changes in connective tissue lead to a high prevalence of dental and jaw anomalies and deformations, with significant increases in indicators with age [3, 6, 12].

It is important to note that disocclusions are not included in the list of life-threatening pathologies, but they can influence the development of severe diseases of the gastrointestinal and respiratory systems, dyslalia, and psycho-emotional disorders. Therefore, early diagnosis and correction of disocclusions, which have pronounced features in congenital collagenopathies requiring an individual approach, are important. In this regard, the study of dental and jaw anomalies and deformations and their connection with congenital genetically determined disorders of connective tissue differentiation is a relevant general medical problem. Some researchers believe that anomalies and deformations of the dental and jaw system are hereditary diseases [3, 24, 32]. From a physiological point of view, all anatomical and morphological structural components of the dental and

jaw system participate in the formation of a permanent bite. Thus, various changes in one of the component parts of the dental and jaw system contribute to the formation of malocclusion [10, 12, 31].

Today, conducted studies have established a high level of prevalence of disocclusion among the population of Russia, which does not show a tendency to decrease, where, on the contrary, a persistent dynamic growth is observed. This confirms the presence of resistant pathogenetic mechanisms for the development of genetically determined disorders of connective tissue differentiation [18, 29, 41]. In this regard, the study of disocclusions has important practical significance in medicine.

Modern aspects of diagnosing local manifestations of connective tissue dysplasia in the maxillofacial area in children. It is important to emphasize that despite extensive research on the problems of congenital collagenopathy, there is currently no unified algorithm of diagnostic criteria and a uniform classification of CTD, which creates difficulties in conducting clinical-epidemiological studies. However, the accepted clinical guidelines for the early diagnosis and treatment of congenital connective tissue differentiation disorders outline the main groups of manifestations of congenital dysgenesis. Based on the results obtained, the severity of CTD is interpreted according to a proposed scale, which allows for the assessment of the practical and diagnostic significance of the scores obtained [30].

During adolescence, the risk of developing decompensated forms of somatic diseases associated with congenital differentiation of connective tissue significantly increases, which is important for their early diagnosis. This pattern is related to the rapid growth of connective tissue during puberty and the growth 'spurt', which leads to the emergence of numerous common and local phenotypic traits of genetically determined connective tissue disorders [15]. The severity of manifestations of congenital collagenopathy largely depends on genetic factors, the deficiency of macro- and micronutrients, vitamins in the body, physical activity, etc., contributing to the manifestation of various dysplastic symptoms and syndromes. In this regard, diagnostic measures for DYST (Dysplastic Syndromes) in children and adolescents should be carried out taking into account the age-related characteristics of the formation of dysplastic phenotypic signs using a wide range of basic and additional research methods [16, 38]. Meanwhile, in individuals aged 35 years and older, the likelihood of additional signs of DYST is minimized, which, in turn, indicates that adults already have a formed set of phenotypic signs of congenital connective tissue differentiation disorders. Recently conducted studies have established the presence of certain features related to the prevalence rates of congenital collagenopathy in modern children, which are significantly higher compared to adults. This is attributed to the deterioration of the environmental situation as well as familial genetic defects that lead to disruptions in the synthesis and maturation of connective tissue [27, 39].

It is important to note that the prevalence of dentofacial anomalies among residents of various regions of Russia has a correlational relationship with the severity of DSD, which does not show a tendency to decrease, but rather demonstrates a trend of dynamic growth, which to some extent confirms the existence of stable mechanisms for the formation and development of this systemic pathology [21, 26]. In this regard, timely dynamic analysis and assessment of local phenotypic traits in the organs and tissues of the oral cavity are of great importance in dentistry, as they correlate with genetically determined disorders of connective tissue differentiation. This situation necessitates the organization and rational conduct of medical and social rehabilitation of dentofacial anomalies and deformations in schoolchildren with congenital collagenopathy. In this regard, early diagnosis and prompt implementation of rehabilitation measures will contribute to preventing dysfunction of the dental-jaw system. When conducting these measures, special attention must be paid to excluding or neutralizing harmful habits (thumb sucking, pacifier use, biting of the tongue, mucosa of the cheeks and lips, constant pressure of the tongue on the teeth, changing the position of the lower jaw) [18, 23]. Meanwhile, 1/3 of young individuals with congenital collagenopathies exhibit dysoccclusions, where retained teeth are often found, which may be associated with manifestations of Down syndrome, Ehlers-Danlos syndrome, and others. According to literature sources, the frequency of manifestations of congenital connective tissue differentiation disorders correlates with anomalies in the shape and number of teeth depending on the severity of congenital collagenopathy. The assessment of the dentofacial manifestations of DSD confirms that in severe cases, there is a significantly increased frequency of anomalies related to the shape or size of teeth, as well as features of tooth eruption. In addition, there is a trend towards an increase in the frequency of caries detection, periodontal diseases, and the prevalence of "non-cariogenic" enamel lesions in the form of various forms of hypoplasia, erosion, wedge defects, and pathological wear at various degrees of severity of DSD [31, 35].

It should be noted that in the case of congenital collagenopathy, a systemic nature of disorders of the organs and tissues of the oral cavity, as well as the jaw-facial area, is determined, which underscores the importance of early diagnosis and prevention. Furthermore, when conducting therapeutic and preventive measures and predicting dental diseases, it is necessary to take into account the morphological and structural features of connective tissue in patients during outpatient-polyclinic and inpatient visits. In this regard, for the prevention of local manifestations of connective tissue dysplasia, an interdisciplinary approach involving other medical specialists is required, which will play a key role in strengthening and preserving the health of the population [11, 17].

It should be noted that there are certain difficulties in diagnosing the symptoms and syndromes of undifferentiated Ehlers-Danlos syndrome (EDS) that are related to the lack of universally accepted diagnostic criteria. Moreover, in clinical practice, the issue of accurately assessing the severity of congenital collagenopathy remains particularly challenging and, in fact, unresolved [1, 2]. One of the important clinical markers of congenital collagenopathy is the involvement of the musculoskeletal system, which includes joint hypermobility, spinal curvature, arachnodactyly, a pectus carinatum, and 'sunken' chest, as well as skin hyper-elasticity. Meanwhile, manifestations of EDS in the gastrointestinal tract include prolapse of internal organs, dysfunction of the hepatobiliary system, etc. [8, 16]. In the diagnosis of manifestations of connective tissue dysplasia (CTD), it is accepted that the presence of three or more external manifestations provides a basis for diagnosing internal organ diseases. Research has established that congenital disorders of connective tissue differentiation are associated with neurovegetative disorders related to vegetative-vascular dystonia, neurotic-like states, and asthenic syndrome with possible panic attacks, which are clinically significant manifestations of genetically determined connective tissue disorders [8, 15, 16].

Thus, the clinical, etiopathogenetic, and diagnostic aspects of the local fea-

tures of dental and skeletal anomalies in school-aged children characterize their prevalence and wide range of manifestations, which require timely diagnostics and the prompt implementation of therapeutic, preventive, and rehabilitation measures that have a positive effect on strengthening and preserving health, as well as improving the quality of life of patients.

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POINT OF VIEW

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THE RELATIONSHIP BETWEEN MARKERS OF METABOLIC SYNDROME AND LEVELS OF SPECIFIC IgG TO FOOD PRODUCTS IN HEALTHY PEOPLE AND WITH METABOLIC SYNDROME

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Due to the steady increase in the incidence of metabolic syndrome (MetS), studying the ways to reduce the risk of its occurrence is an important task for modern medicine. The aim of the study is to identify the relationship of MetS markers with the levels of specific IgG to various products, as well as to assess the relationship of the content of proinflammatory cytokines and C-reactive protein with MetS. It is shown that for the examined individuals with MetS, more direct correlations are recorded and most often - with the glucose level. Many products can provoke postprandial hyperglycemia, which in a practically healthy person will not cause significant disturbances, but with MetS, a failure of glucose and lipid homeostasis in combination with insulin resistance does not allow effective correction of blood glucose levels. Thus, when introducing elimination diets for MetS, it is necessary to take into account the possibility of postprandial hyperglycemia in this group of people, monitor glucose and insulin levels to prevent the development of insulin resistance.

Keywords: food antigens, metabolic syndrome, specific IgG, correlation relationships.

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