УДК 616-018.2-007.17-06:616-008.9
https://doi.org/10.20538/1682-0363-2024-3-136-144

Hormonal and metabolic disorders in connective tissue dysplasia

Bespalova I.D., Chomaeva Z.S., Teteneva A.V., Koshchavtseva Yu.I., Mitrichenko U.M., Romanov D.S., Nesterovich S.V., Poljakova D.V., Bukreeva E.B., Sorokina T.V., Kalyuzhina E.V., Tetenev K.F., Karzilov A.I., Mesko P.E., Boyarko V.V., Chernogoryuk G.E., Chernyavskaya G.M.

Siberian State Medical University
2, Moscow Trakt, Tomsk, 634050, Russian Federation

ABSTRACT

The lecture considers the results of research conducted by Russian and foreign scientists concerning the characteristics of all types of metabolic disorders and hormonal imbalance in undifferentiated connective tissue dysplasia (CTD). Understanding the role of hormonal and metabolic disorders in the development and course of diseases associated with CTD is of great importance for the development of pathogenetically grounded algorithms for the diagnosis, treatment, and prevention of emergency conditions.

Keywords: connective tissue dysplasia, metabolic disorders, hormonal status

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

For citation: Bespalova I.D., Chomaeva Z.S., Teteneva A.V., Koshchavtseva Yu.I., Mitrichenko U.M., Romanov D.S., Nesterovich S.V., Poljakova D.V., Bukreeva E.B., Sorokina T.V., Kalyuzhina E.V., Tetenev K.F., Karzilov A.I., Mesko P.E., Boyarko V.V., Chernogoryuk G.E., Chernyavskaya G.M. Hormonal and metabolic disorders in connective tissue dysplasia. *Bulletin of Siberian Medicine.* 024;23(3):136–134. https://doi.org/10.20538/1682-0363-2024-3-136-144.

Гормонально-метаболические нарушения при дисплазиях соединительной ткани

Беспалова И.Д., Чомаева З.С., Тетенева А.В., Кощавцева Ю.И., Митриченко У.М., Романов Д.С., Нестерович С.В., Полякова Д.В., Букреева Е.Б., Сорокина Т.В., Калюжина Е.В., Тетенев К.Ф., Карзилов А.И., Месько П.Е., Боярко В.В., Черногорюк Г.Э., Чернявская Г.М.

Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

В лекции обсуждаются результаты исследований отечественных и зарубежных ученых, касающиеся особенностей нарушений всех видов обмена и гормонального дисбаланса при недифференцированной дисплазии соединительной ткани (ДСТ). Понимание роли гормонально-метаболических нарушений в развитии и

✉ *Bespalova Inna D.,* innadave@mail2000.ru

течении ассоциированных с ДСТ заболеваний имеет большое значение для разработки патогенетически обоснованных алгоритмов диагностики, лечения и профилактики неотложных состояний.

Ключевые слова: дисплазия соединительной ткани, нарушения обмена, гормональный статус

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Беспалова И.Д., Чомаева З.С., Тетенева А.В., Кощавцева Ю.И., Митриченко У.М., Романов Д.С., Нестерович С.В., Полякова Д.В., Букреева Е.Б., Сорокина Т.В., Калюжина Е.В., Тетенев К.Ф., Карзилов А.И., Месько П.Е., Боярко В.В., Черногорюк Г.Э., Чернявская Г.М. Гормонально-метаболические нарушения при дисплазиях соединительной ткани. *Бюллетень сибирской медицины.* 2024;23(3):136–134. https://doi.org/10.20538/1682-0363-2024-3-136-144.

INTRODUCTION

The concept of connective tissue dysplasia (CTD) implies structural and functional disorders of connective tissue and their systemic manifestations in multiple organs. CTD syndrome is marked by a number of specific pathological conditions of connective tissue, which are designated as genetic disorders of collagen metabolism, since they are associated with congenital metabolic and structural defects of collagen. In addition to a number of hereditary syndromes described in detail (Marfan syndrome, Ehlers – Danlos syndromes, Stickler syndrome, etc.), pathological changes in the form of incomplete, suppressed, undifferentiated forms combined into a group of undifferentiated connective tissue diseases (UCTD) are of great social and medical significance [1]. They do not meet the diagnostic criteria of the above listed genetically determined syndromes, but at the same time they are characterized by a set of signs indicating the presence of connective tissue disease with multiple organ damage [2].

Due to the systemic nature of the manifestations, the symptoms of UCTD are of interest for various clinicians, including not only pediatricians and therapists, but also specialty physicians, such as cardiologists, surgeons, gynecologists, urologists, pulmonologists, etc. [3]. Researchers are interested in studying and making practical use of the knowledge obtained about this pathological process because of its high prevalence, the diversity of phenotypic characteristics, the trend toward a progressive course and adverse outcomes, and the relevance of the search for prognostically significant markers of a severe course and complications of associated pathology [4].

Currently, there is no generally accepted classification of UCTD that would be recognized by all researchers and clinicians. No consensus was reached regarding diagnostic criteria, terminology, or assessment of the severity of this condition. However, patients with UCTD represent a large group with multiple organ disorders of varying severity and require an interdisciplinary approach in their medical care [3–6].

METABOLIC DISORDERS IN CTD

The formation of this pathological process is based on a genetically determined defect in the development of the mesenchymal matrix of the body. It is accompanied by a decrease in the strength of the connective tissue framework supporting systems and organs, with subsequent morphofunctional disorders closely related to changes in the hormonal and metabolic state [7]. Hormonal and metabolic parameters can form a panel of biological markers of CTD at the preclinical stage, which determines the relevance of this literature review.

According to a number of authors, CTD is a hereditary metabolic anomaly, which is based on impaired formation and maturation of connective tissue structures in the body, which leads to the development of dysplastic changes in tissues and contributes to the occurrence of diseases of the musculoskeletal system and internal organs [8]. It is believed that impaired synthesis of collagen, the main structural element of connective tissue, underlies organ dysfunction in CTD. Proteins including

glycosaminoglycans – glycoproteins perform a structural function in various mucous secretions and cell membranes, being an important component of the intercellular matrix. Intermolecular bond disruption leads to collagen disorganization [9]. In practice, the state of collagen is assessed by the level of a number of amino acids – its structural components in the biological media of the body. Oxyproline is one of the main amino acids of collagen, a biomarker reflecting the catabolism of this protein. An increase in the concentration of oxyproline in a 24-hour urine test is associated with the severity of CTD and an increased level of other amino acids in the blood, namely hydroxyproline, lysine, and proline [3].

The presence of CTD significantly affects tolerance and adaptation to exercise. Patients with UCTD often suffer from exercise-related musculoskeletal disorders and are predisposed to re-injury [10]. In this regard, the presence of CTD implies a personalized approach to the exercise regime in these patients.

According to a number of authors, the asthenic body type associated with malnutrition is one of the most important phenotypic signs of CTD and is statistically significantly more often observed in this pathology than in the general population [11]. Protein – energy malnutrition in UCTD is registered in 40% of cases and is accompanied by all types of metabolic disorders, which makes active search for mechanisms that explain this association relevant [12]. There is a point of view that nutrient deficiency as an adaptation mechanism in the prenatal period leads to complex metabolic changes that determine collagenopathy and associated dysfunction of body systems. Since the hypothalamic – pituitary – adrenal axis (HPA axis) represents one of the adaptational systems of the body [13], the features of the gestational period can preset the state of the HPA axis and contribute to an unfavorable prognosis of developing diseases in adulthood.

This concept is highlighted by literature data that low body weight of newborns is associated with arterial hypertension in both children and adults, as well as with increased excretion of androgens and glucocorticoids. Increased activity of the HPA axis contributes to more active catabolic processes with progressive body weight loss in patients with hypoproteinemia and hypoalbuminemia. High sympathetic tone ensures an increase in the intensity of the basal metabolic rate and a sharp decrease in energy expenditure. Increased catabolism in malnutrition is characterized by depletion of glycogen and fat depots at the beginning. Then, with a significant deficiency of nutrients, protein breakdown occurs in muscle tissue, and the level of transport proteins in the blood decreases. Protein deficiency leads to immune suppression associated with both limited synthesis of immunoglobulins and ineffective antioxidant defense, which together contribute to deficiency of intracellular energy, disruption of adequate transport of micronutrients, and damage to cell membranes [12].

Protein metabolism disorders in CTD are also manifested by changes in the vascular and platelet component of hemostasis, as evidenced by the presence of platelet function disorders in most children [14]. The relationship between the severity of anemia and the number of clinical signs of CTD was found. This is confirmed by low levels of hemoglobin, red blood cells, ferritin, and serum iron [15]. Researchers consider different mechanisms of anemia development in CTD. However, most tend to believe that disruption of submembrane cytoskeleton in red blood cells plays a crucial role in reducing the life span of red blood cells, which significantly affects elasticity and reduces their elastic deformation when passing through the microvasculature [16, 17]. In particular, it has been shown that an imbalance of antioxidant enzymes (superoxide dismutase and catalase) is observed in adolescents with UCTD. In turn, this can lead to the accumulation of aggressive hydroperoxides in the blood plasma, which damage blood cells, and contribute to the development of lipid peroxidation in erythrocyte membranes [18].

Neonatal body weight deficiency was also found to be associated with insulin resistance and impaired glucose tolerance afterwards. Since skeletal muscles and adipose tissue are the main peripheral tissues affected by insulin in adults, body weight deficiency and malnutrition at birth can be considered as adaptive manifestations [19]. However, researchers from Donetsk National Medical University showed that in children with UCTD and functional dyspepsia (FD), insulin and cortisol levels were significantly lower than in children without signs of CTD and in healthy individuals [20]. Increased catabolism in people with body weight deficiency and related stress are also associated with a decrease in enzyme

activity and insulin synthesis, and an increase in the cortisol / insulin index is observed.

In malnutrition associated with CTD, energy metabolism changes significantly, mainly from carbohydrate to lipid. Moderate malnutrition is accompanied by increased fat breakdown, in which non-esterified fatty acids (NEFA) become an important source of energy. Under these conditions, the biosynthesis of fatty acids from cholesterol is activated, which is necessary for the satisfactory functioning of the digestive system and the complete synthesis of corticosteroids, which regulate adaptation reactions. With more severe protein – energy deficiency and grade III malnutrition in patients with slowing fat catabolism, the absorption of NEFA worsens, and the level of cholesterol and its fractions in the blood decreases, which contributes to disrupted structure and impaired function of cell membranes and a decrease in the concentrations of corticosteroids and fatty acids [12].

Impaired lipid metabolism in CTD is a key link in the pathogenesis of many diseases in people of any age. It is believed that the content of free and bound fatty acids in the blood serves as an additional biomarker of CTD [3]. Researchers discuss the significance of the pathology of cell membranes and lipid and fatty acid composition of blood plasma in the pathogenesis of arterial hypertension and other cardiovascular diseases [21]. It is now known that deficiency of polyunsaturated omega-3 fatty acids underlies the occurrence of cardiovascular pathology. Cardiovascular diseases in children are some of the most common childhood pathologies [22, 23]. Changes in the architectonics of the heart and great vessels in young people with CTD and their dysfunction are explained, among other things, by impaired lipid metabolism.

Impaired mineral metabolism is another important link in the pathogenesis of CTD, given the essential role of macro- and microelements in the formation of the connective tissue structure. According to the literature data, the majority of patients with CTD experience changes in the macro- and microelement composition of biological media. Thus, in persons with CTD, deficiency of the following elements has been described: silicon, selenium, potassium, calcium, copper, manganese, magnesium, and zinc. All of the above elements are more or less involved in bone mineralization, collagen synthesis, and maturation [24]. A comparative analysis of clinical and laboratory data from underweight children with and without CTD showed that in the absence of statistically significant differences in anthropometric parameters, including bioelectrical impedance analysis, in patients without CTD, the content of mineral substances in the body was within the reference values [25].

The analysis of the literature data showed that researchers mainly focus on studying the role of calcium and magnesium in the pathogenesis of morphofunctional disorders associated with CTD [26]. The deficiency of these elements is associated not only with a decrease in the strength of the bone skeleton according to densitometry, but also with a disruption of the vascular wall structure and impaired function of the nervous system. At the same time, low magnesium levels negatively correlate with the severity and number of phenotypic signs of CTD [27, 28]. It is also known that hypomagnesemia underlies the development of insulin resistance and increases the risk of impaired glucose tolerance. Often, children with CTD exhibit deficiency of not just one, but a number of microelements. As expected, the most frequently described combination is deficiency of calcium and magnesium, however, some researchers have described combined deficiency of microelements which actively participate in collagen formation, such as zinc, selenium, iodine, and copper [29].

HORMONAL DISORDERS IN CTD

The above mentioned metabolic disorders in CTD have complex hormonal regulation, which is confirmed by the results of research characterizing hormonal imbalance in CTD. Since diabetes mellitus (DM) is an extreme manifestation of carbohydrate metabolism disorders and the formation of vascular and neurological complications in this pathology is associated with the involvement of connective tissue in the pathological process, an attempt was made to study the features of the association between UCTD and DM. It was found that UCTD negatively affects the prognosis and course of type 1 diabetes [30] and type 2 diabetes, which is manifested by earlier depletion of regulatory mechanisms and decreased opportunities for rehabilitation and psychological adaptation. UCTD in combination with type 2 diabetes is considered as an independent

cardiovascular risk factor for cardiac arrhythmias, valvular dysfunction, and autonomic imbalance, contributing to sympathicotonia, electrical instability of the myocardium and prolonged PQ interval and increasing the risk of sudden cardiac death [31].

The analysis of the results of a large-scale study on the functional state of the main body systems demonstrated that patients with UCTD were more likely to have uncompensated DM and developed late complications two times more often and 2 to 3 years earlier than patients without CTD [32]. Symptoms of CTD were regarded as predictors of the development of comorbid pathology in patients with type 2 diabetes, which primarily implied cardiovascular and musculoskeletal diseases [32]. In children and adolescents with type 1 diabetes and CTD, complications, such as diabetic neuropathy and nephropathy, develop earlier from the onset of the disease and have a more severe course than in patients without dysplasia, which allows to consider them as a special risk group [33].

Thyroid pathology is considered to be the most frequently diagnosed pathology in patients with CTD. Autoimmune thyroiditis occurs in more than 37% of patients, which is significantly more common than in the control group [34]. Thyroid hormones are involved in the regulation of growth and skeletal maturation [4]. It is known that free thyroxine and triiodothyronine activate the synthesis of type I collagen and osteocalcin in bones. The biological effects of thyroid hormones and thyroid-stimulating hormone include inhibition of fibroblast proliferation and chondrocyte differentiation in various types of connective tissue, which underlies an increase in bone density in hypothyroidism [35].

Krasnodar researchers also showed that autoimmune pathology of the thyroid gland and basal and/or postprandial hyperinsulinemia are the most common of all endocrine diseases identified in patients with UCTD, diagnosed in 37.7% and 43.4% of cases, respectively, which is statistically significantly higher than in the control group [34]. Various research groups have shown that in young people with UCTD, autoimmune thyroiditis is diagnosed in 32.5% of cases and in women of fertile age – in 42.9% of cases, which is more often than in the general population. At the same time, the frequency and severity of visceral, osteoarticular, and skin phenotypic signs of UCTD are more significant than in individuals with UCTD who do not have thyroid pathology. Also, in this category of people, higher titers of antibodies to thyroid peroxidase and thyroglobulin are recorded, in contrast to healthy controls, which allows to consider all patients with UCTD as a risk group for the development of autoimmune thyroid pathology [36]. The high risk of developing autoimmune thyroiditis and hypothyroxinemia in joint hypermobility syndrome makes it reasonable to examine patients in order to diagnose thyroid dysfunction that would require subsequent targeted personalized therapy and iodine prophylaxis in this target group [35].

Impaired development of the reproductive system in adolescents is a consequence of UCTD. In girls, the most common problem is menstrual dysfunction, characterized by early menarche, hypomenorrhea and amenorrhea, as well as by uterine bleeding during puberty. In turn, hormonal and metabolic changes accompanied by menstrual dysfunction aggravate the course of CTD. The assessment of the hormonal status of teenage girls with UCTD and menstrual disorders showed that younger girls (11–13 years old) with UCTD had an increased level of follicle-stimulating hormone (FSH) and decreased content of luteinizing hormone (LH), the LH / FSH index was reduced up to 0.7, which corresponds to gonadotropin function in infants and luteal phase deficiency.

In a group of adolescent girls with UCTD (14–16 years old), 55% were also diagnosed with immaturity of the reproductive system, which may be associated with UCTD (pubertal maturity index < 1.0). However, 45% of patients had high sexual maturity rating (2.0–2.5) [37]. The hormonal status of adolescents with UCTD of both sexes was characterized by a higher level of gonadotropins than in healthy peers. Moreover, in patients with minimal manifestations of dysplasia, the FSH level was significantly higher than in the control group and in patients with moderate and severe dysplasia, and the LH level was significantly higher than in the control group.

However, in severe dysplasia, gender-specific hormonal status was revealed. Thus, in the group of girls with severe CTD, FSH levels were significantly reduced and had an inverse correlation with the severity of dysplasia. In the group of boys, elevated FSH and LH levels were noted in mild UCTD, while

patients with severe UCTD had low concentrations of the two hormones [37]. This indicates that in severe cases, inhibition of the gonadotropin function of the pituitary gland occurs, whereas with minimal dysplastic changes, gonadotropin activity is high. Researchers explain hyperprolactinemia in adolescents with UCTD as a reaction caused by an inadequate response of the body to stress. It is known that patients with UCTD have a cluster of emotional, personal and temperament characteristics, which also requires in-depth study [38, 39].

The presence of CTD in boys may also underlie delayed puberty, including symptoms that require surgery, such as micropenis, hypermobility, testicular hypoplasia, and varicocele [40]. Varicocele can also be one of the manifestations of CTD in men. During the examination of 721 adolescent patients diagnosed with varicocele, it was found that patients who had recurrent varicocele had more than seven verified diagnostic signs of CTD, which makes it possible to consider UCTD as a cause of varicocele recurrence. A 10–100 increase in the level of sex hormones (estradiol and testosterone) in the blood of the pampiniform plexus was characteristic of such patients, which may indicate hormonal regulation in this pathology [40].

The presence of UCTD in patients is associated with a high risk of gestational complications, such as threatened miscarriage and incipient abortion, cervical incompetence, premature rupture of membranes, and retrochorial hematoma [41, 42]. The examination of 80 pregnant women with threatened preterm labor and cervical incompetence revealed the prevalence of phenotypic signs of UCTD in more than 90% of cases [43]. The above-described features of hormonal imbalance and sexual development in adolescents may partially explain the data obtained on the negative impact of UCTD on the reproductive function of both women and men.

Malnutrition is a symptom complex of great medical and social significance due to a high risk of adverse prognoses associated with the presence of this syndrome. It is believed that a large part of metabolic disorders is genetically determined, and mutations of genes encoding adipokines and their receptors are pivotal. Adipokines are hormone-like substances, secreted by adipose tissue, an imbalance of which can lead to metabolic disorders. The biological effects of adipokines in abdominal obesity, metabolic syndrome, and associated pathologies have been well studied [44, 45]. Since there is a lack of data on the pathogenesis of malnutrition in patients with CTD and high frequency and severity of nutritional status disorders, an attempt was made to assess the level of a number of adipokines and their receptors in patients with CTD and malnutrition. It was found that in such patients, the adipokine profile was characterized by a decrease in the levels of leptin and resistin in the blood and an increase in the concentration of soluble leptin receptors and adiponectin [19].

CONCLUSION

Thus, CTD contributes to the formation of pathology of various systems and organs and has a wide variety of manifestations. Metabolic disorders and hormonal imbalance are not only a manifestation of this pathology, but also underlie the progression of associated clinical conditions.

Understanding the role of hormonal and metabolic disorders in the development and course of diseases associated with CTD is of great importance for the development of diagnostic algorithms based on pathogenetics and targeted treatment, including metabolic therapy and effective personalized algorithms for preventing the progression and complications of the pathological process which would improve the quality of life.

REFERENCES

1. Kadurina T.I., Abbakumova L.N. Assessment of the severity of undifferentiated connective tissue dysplasia in children. *Medical News of the North Caucasus.* 2008;(2):15–20 (in Russ.).
2. Kotlyarov V.L., Kalinina M.A., Kozlovskaya G.V., Shimonova G.N. Congenital connective tissue dysplasia and small heart abnormalities in children as a risk factor for the development of mental pathology. *Russian Journal of Woman and Child Health.* 2022;5(4):346–350 (in Russ.). DOI: 10.32364/2618-8430-2022-5-4-346-350.
3. Nokhsorova M.A., Borisova N.V., Ammosova A.M. The possibility of diagnosing undifferentiated connective tissue dysplasia using biological markers. *Journal of New Medical Technologies. Electronic edition.* 2019;(4):138–143 (in Russ.). DOI: 10.24411/2075-4094-2019-16435.
4. Bogomolova I.K., Plotnikova M.I. The role of macro- and microelements in undifferentiated connective tissue dysplasia in children. *The Transbaikalian Medical Bulletin.* 2021;(3):59–69 (in Russ.). DOI: 10.52485/19986173-2021-3-59.
5. Teteneva A.V., Bespalova I.D., Serdyukov N.A., Bodrova T.N., Vesnina Zh.V., Tonkikh O.S., et al. Structural and functional disorders of the bronchopulmonary system in patients with connective tissue dysplasia and malnutrition. *Siberian Medical*

Review. 2023;(6):33–40 (in Russ.). DOI: 10.20333/25000136-2023-6-33-4.
6. Vesnina Zh.V., Anashbaev Zh.Zh., Teteneva A.V., Krivonogov N.G., Bespalova I.D., Sazonova S.I., et al. Radionuclide methods in the assessment of pulmonary perfusion and ventilation in patients with connective tissue dysplasia. *Bulletin of Siberian Medicine*. 2022;21(3):22–27 (in Russ.).
7. Abdukadirova N.B., Rabbimova D.T., Khayatova Z.B. The role of connective tissue dysplasia in the development of pathology of various body systems. *Journal of Siberian Medical Sciences*. 2020;(3):126–135 (in Russ.). DOI: 10.31549/2542-1174-2020-3-126-135.
8. Akatova E.V., Anikin V.V., Arsentiev V.G., et al. Undifferentiated connective tissue dysplasia (draft clinical guidelines). *Therapy.* 2019;7(33):9–42 (in Russ.). DOI: 10.18565/therapy.2019.7.9-42.
9. Pervykh S.L., Karpova E.I. Etiological diversity in the development of connective tissue dysplasia. *RMJ.* 2023;6:13–15 (in Russ.).
10. Nikolenko V.N., Oganesyan M.V., Vovkogon A.D., Cao Y., Churganova A.A., Zolotareva M.A. et al. Morphological signs of connective tissue dysplasia as predictors of frequent post-exercise musculoskeletal disorders. *BMC Musculoskelet Disord.* 2020;21(1):660. DOI: 10.1186/s12891-020-03698-0.
11. Dvornichenko M.V., Gereng E.A., Karpova M.P., Saprina T.V., Chernyakhovskaya D.V., Nasibov T.F. Features of anthropometric indicators as a phenotypic characteristic of undifferentiated connective tissue dysplasia syndrome. *Siberian Journal of Clinical and Experimental Medicine.* 2023;38(4):159–166 (in Russ.). DOI: 10.29001/2073-8552-2023-38-4-159-166.
12. Nechaeva G.I., Druk I.V., Lyalyukova E.A. Protein-energy deficiency in clinical practice. *Experimental and Clinical Gastroenterology.* 2013;(7):23–26 (in Russ.).
13. Ryzhevol E.V., Parkhomchuk D.S., Larkova I.V., Bulgakova O.S. Psychophysiological mechanisms of tension and stress (review of Russian sources, 2005–2021). *Bulletin of Psychophysiology.* 2021;4:19–36 (in Russ.). DOI: 10.34985/r4281-7630-0414-w.
14. Skudarnov E.V., Vykhodtseva G.I., Kolesnikova O.I., Strozenko L.A., Malyuga O.M., Mironenko I.I., et al. Thrombocytopathies in children with undifferentiated connective tissue dysplasia. *Russian Bulletin of Perinatology and Pediatrics.* 2021;66(4):348 (in Russ.).
15. Shodikulova G.Z., Mirzaev O.V., Fozilova M.Sh. The condition of the peripheral blood system of patients with connective tissue dysplasia. *Achievements of Science and Education.* 2022;1(81):61–66 (in Russ.).
16. Ivanova I.I., Makarova I.I., Ibragimova Sh.M., Saidalieva K.D., Sultonova F.S. Structural and functional features of the erythroid germ in patients with connective tissue dysplasia. *Ural Medical Journal.* 2022;21(6):136–143 (in Russ.). DOI: 10.52420/2071-5943-2022-21-6-136-143.
17. Proshin A.N., Mashin V.V., Belova L.A., Belov D.V. Structure of intracranial veins and elastic-viscous properties of red blood cell membranes in adolescents with connective tissue dysplasia. *Ul'yanovskiy Mediko-Biologicheskiy Zhurnal.* 2021;(3):47–60 (in Russ.). DOI: 10.34014/2227-1848-2021-3-47-60.
18. Pochynok T.V., Vasiukova M.M., Kudlatska-Tyshko I.S. Peroxidative degradation of proteins and lipids in undifferentiated connective tissue dysplasia in children, Ukraine. *Narra J.* 2021;1(2):e41. DOI: 10.52225/narraj.v1i2.41.
19. Nechaeva G.I., Nadey E.V., Lyalyukova E.A., Tsikunova Y.S. Undernourishment in patients with connective tissue dysplasia: the role of proinflammatory cytokines and adipokines, and genetic factors. *International Heart and Vascular Disease Journal.* 2017;5(16):39–45 (in Russ.). DOI: 10.24412/2311-1623-2017-16-39-45.
20. Poshekhonova Yu.V. Effect of connective tissue dysplasia on the hormonal background of children with functional dyspepsia. *Kursk Scientific and Practical Peer-Reviewed Journal "Humans and Their Health".* 2018;(3):32–37 (in Russ.). DOI: 10.21626/vestnik/2018-3/05.
21. Vershinina M.V., Nechaeva G.I., Gudilin V.A. Relative cardiovascular risk in young patients with connective tissue dysplasia. *Therapy.* 2020;6(40):40–45 (in Russ.). DOI: 10.18565/therapy.2020.6.40-44.
22. Loginova E.N., Nechaeva G.I., Dakuko A.N., Bogatyrev I.V. Phenotypic features of patients with arrhythmic syndrome and undifferentiated connective tissue dysplasia. *Medical News of the North Caucasus.* 2022;17(4):426–427 (in Russ.).
23. Kudryashova M.V. Myxoid heart disease: clinical, immunological, hemodynamic aspects. *Bulletin of the Council of Young Scientists and Specialists of the Chelyabinsk Region.* 2021;1(36):21–33 (in Russ.).
24. Nechaeva G.I., Drokina O.V., Druk I.V., Vershinina M.V., Lyalyukova E.A., Kolmenkova I.V. Main approaches in treatment of patients with connective tissue dysplasia. *Lechaschi Vrach Journal.* 2014;(8):70 (in Russ.).
25. Keleynikova A.V., Titova O.N., Matinyan I.A., Taran N.N., Zubovich A.I., Strokova T.V. Nutritional status of children with undernutrition. *Medical alphabet.* 2021;(21):51–57 (In Russ.). DOI: 10.33667/2078-5631-2021-21-51-57.
26. Kytko O.V., Dydykina I.S., Sankova M.V., Kryucko P.V., Chilikov V.V. Pathogenetic aspects of magnesium deficiency in connective tissue dysplasia syndrome. *Problems of Nutrition.* 2020;89(5):35–43 (in Russ.). DOI: 10.24411/0042-8833-2020-10064.
27. Rozhkova N.S., Kovalenko A.D. Phenotypic markers of connective tissue dysplasia in the practice of a general practitioner. *Bulletin of Medical Internet Conferences.* 2021;11(7):155–157 (in Russ.).
28. Akimova A.V., Popov A.A., Palabugina P.A. Assessment of the association of undifferentiated connective tissue dysplasia, number of fractures and the risk of magnesium deficiency in young men. *Osteoporosis and Bone Diseases.* 2020;23(1):25 (in Russ.).
29. Smetanin M.Yu., Andreev S.Yu., Pimenov L.T., Chistyakova T.V., Vasilyeva O.A. Estimation of carbohydrate metabolism, hormonal and thyroid status indices in patients with connective tissue dysplasia syndrome. *Perm Medical Journal.* 2011;28(6):70–74 (in Russ.).
30. Mazepa S.I., Kotovshchikova E.F., Veitsman I.A., Lomakina N.A., Nechaeva M.N. Features of the course of type 1 di-

abetes mellitus and its complications against the background of undifferentiated connective tissue dysplasia. *Kazan Medical Journal.* 2023;104(6):877–884 (in Russ.). DOI: 10.17816/KMJ340788.
31. Maslova I.S., Kournikova I.A. Peculiarities of diabetes mellitus in combination with connective tissue disorders. *Basic Research.* 2010;(8):41–45 (in Russ.).
32. Chernyshova T.E., Kournikova I.A., Maslova I.S. Connective tissue dysplasia: prognostic value in diabetology. *Kuban Scientific Medical Bulletin.* 2009;46(111):76–79 (in Russ.).
33. Kenner V.E. The incidence of mesenchymal dysplasia in patients with type 1 diabetes mellitus. The effect of mesenchymal dysplasia on the course of type 1 diabetes mellitus. *Scientist (Russia)*. 2019;4(10):13 (in Russ.).
34. Ivanova L.A., Korol I.V., Vytkalova N.V. Syndrome of undifferentiated connective tissue dysplasia and endocrine pathology. *Kuban Scientific Medical Bulletin.* 2008;5(104):63–68 (in Russ.).
35. Saneeva G.A. Structure and clinical significance of thyroid pathology in case of tissue dysplasia and hypermobility syndrome. *International Scientific Research Journal.* 2017;1-1(55):160–163 (in Russ.). DOI: 10.23670/IRJ.2017.55.042.
36. Smetanin M.Yu., Pimenov L.T., Chernyshova T.E., Kononova N.Yu. The functional status of the thyroid gland in women with connective tissue dysplasia. *Therapy.* 2019;2(28):71–74 (in Russ.). DOI: 10.18565/therapy.2019.2.71-74.
37. Zoloto E.V. Features of the hormonal status in adolescent girls with menstrual disorders and undifferentiated connective tissue dysplasia. *Medical and Social Problems of the Family.* 2019;24(1):23–27 (in Russ.).
38. Zakharova I.N., Tvorogova T.M., Solovyova E.A., Stepurina L.L., Vorobyova A.S. Connective tissue dysplasia: a risk factor for osteopenia in children and adolescents. *Medical Council.* 2020;(1):30–40 (in Russ.). DOI: 10.21518/2079-701X-2020-1-30-40.
39. Galeeva V.R. The psychological state of young people with undifferentiated connective tissue dysplasia. *Scientist.* 2022;22(4):179–180 (in Russ.).
40. Kotov S.V., Korochkin N.D., Klimenko A.A. Recurrent varicocele. *Urology Herald*. 2021;9(2):132–141 (in Russ.). DOI: 10.21886/2308-6424-2021-9-2-132-141.
41. Kononenko I.S., Zhukova N.P. Undifferentiated connective tissue dysplasia as a significant risk factor of pregnancy loss. *Meditsinskie Novosti.* 2020;5(308):55–57 (in Russ.).
42. Novitskaya T.V. Undifferentiated connective tissue dysplasia as a risk factor of gestational complications. *Journal of the Grodno State Medical University*. 2022;20(6):637–641 (in Russ.). DOI: 10.25298/2221-8785-2022-20-6-637-641.
43. Ibadova T.V., Maliar V.V., Maliar V.V., Maliar V.V. Epidemiology of the prevalence of phenotopic signs undifferentiated connective tissue dysplasia syndrome in woman with miscarriages. *Wiad Lek.* 2021;74(4):880–883.
44. Bespalova I.D. Leptin as an inducer of inflammation and oxidative stress by metabolic syndrome. *Bulletin of Siberian Medicine.* 2014;13(1):20–26 (in Russ.).
45. Bespalova I.D., Ryazantseva N.V., Kalyuzhin V.V., Ossikhov I.A., Murashev B.Yu., Medyantsev Yu.A., et al. Gender features of interaction of hormonal activity of adipose tissue and proinflammatory status in hypertensive disease with metabolic syndrome. *Bulletin of Siberian Medicine.* 2014;13(5):12–19 (in Russ.).

Authors' information

Bespalova Inna D. – Dr. Sci. (Med.), Head of the Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, innadave@mail2000.ru, http://orcid.org/0000-0002-4513-6329

Chomaeva Zauata S. – Resident, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, chomaeva.zs@ssmu.ru

Teteneva Anna V. – Dr. Sci. (Med.), Professor, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, anna.dubodelova@mail.ru, http://orcid.org/0000-0002-4323-2798

Koshchavtseva Yulia I. – Teaching Assistant, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, kossy09@mail.ru, http://orcid.org/0000-0001-5260-4832

Mitrichenko Ulyana M. – Post-Graduate Student, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, strashkova.um@ssmu.ru, http://orcid.org/0000-0001-6091-4849

Romanov Dmitry S. – Post-Graduate Student, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, romanovds92@yandex.ru, http://orcid.org/0009-0002-2028-4963

Nesterovich Sofya V. – Cand. Sci. (Med.), Chief Physician of University Clinics, Siberian State Medical University, Tomsk, nesterovich.sv@ssmu.ru, http://orcid.org/0000-0003-2098-2964

Poljakova Daria V. – Deputy Chief Physician for Medical Units, Siberian State Medical University, Tomsk, polyakova.dv@ssmu.ru

Bukreeva Ekaterina B. – Dr. Sci. (Med.), Professor, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, kbukreeva@mail.ru, http://orcid.org / 0000-0002-7699-5492

Sorokina Tatyana V. – Teaching Assistant, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, sorokina.tv@ssmu.ru, http://orcid.org/0000-0002-6264-4632

Kalyuzhina Elena V. – Dr. Sci. (Med.), Professor, Advanced Therapy Division with Rehabilitation, Physiotherapy and Sports Medicine Course, Siberian State Medical University, Tomsk, kalyuzhina.ev@ssmu.ru, http://orcid.org/0000-0002-7978-5327

Tetenev Konstantin F. – Cand. Sci. (Med.), Associate Professor, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, tetenev.kf@ssmu.ru, http://orcid.org/0000-0002-5306-6589

Karzilov Alexander I. – Dr. Sci. (Med.), Professor, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, karzilov@mail.ru, http://orcid.org/0000-0002-3919-7205

Mesko Pavel E. – Cand. Sci. (Med.), Associate Professor, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, mpe106@mail.ru

Boyarko Valentina V. – Cand. Sci. (Med.), Associate Professor, Introduction into Internal Diseases Division with Therapy Course of the Pediatrics Department, Siberian State Medical University, Tomsk, vvboyarko@mail.ru, http://orcid.org/0000-0002-5700-1640

Chernogoryuk Georgy E. – Dr. Sci. (Med.), Professor, Advanced Therapy Division with Rehabilitation, Physiotherapy and Sports Medicine Course, Siberian State Medical University, Tomsk, e-mail: chernogoryuk.ge@ssmu.ru, http://orcid.org/0000-0001-5780-6660

Chernyavskaya Galina M. – Dr. Sci. (Med.), Professor, Advanced Therapy Division with Rehabilitation, Physiotherapy and Sports Medicine Course, Siberian State Medical University, Tomsk, chernyavskaya.gm@ssmu.ru, http://orcid.org/0000-0003-0105-2307

(✉) **Bespalova Inna D.,** innadave@mail2000.ru

Received 06.02.2024;
approved after peer review 13.05.2024;
accepted 25.05.2024