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Review Article

Peculiarities of Menstrual and Reproductive Function Formation in Girls with Connective Tissue Dysplasia (Literature Review)

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Abstract

The review below highlights an acute problem - the formation of menstrual and reproductive function in girls of puberty against the background of mesenchymal pathology - undifferentiated forms of connective tissue dysplasia and options for drug correction (trace elements, hormonal drugs, adaptogens).

Keywords: *Menstrual and Reproductive Function; Trace Elements; Hormonal Drugs; Adaptogens*

Introduction

The term connective tissue dysplasia is used to describe genetically determined syndromes and symptom complexes characterized by defects in fibrous structures and the basic substance of the connective tissue, leading to impaired organ and system formation [1].

For many years connective tissue dysplasia (CTD) has been studied by scientists mainly from the Russian Federation, represented by both monogenic hereditary forms (Marfan syndrome, variants of the Ehlers-Danlos syndrome, epidermolysis bullosa, etc.), and undifferentiated forms - uCTD [1]. In recent years, much attention has been paid to uCTD, which is associated with its high prevalence in the population, which, according to different authors, varies from 26 to 80% [1,2]. The percentage of pronounced forms of mesenchymal pathology, meaning the presence of severe damage to the connective tissue from several systems, is about 5 - 10% [3]. Signs of uCTD tend to manifest progressively throughout life: during the neonatal period, the clinical manifestation of symptoms is minimal; by the age of 4 - 5, mainly prolapses of the heart valves begin to form; by 5 - 7 years of age - deformities of the chest and spine, flat feet, myopia; in adolescence and young age - vascular disease [3,4]. The critical period of maximum phenotypic manifestations of CTD is puberty when the increase in the number of signs of connective tissue failure can be more than 30%. The severity of CTD in different age periods is explained by the degree of correlation of individual tissue structures in these periods of development of the human body. The highest concentration

of glycoproteins is noted in the embryonic period, proteoglycans - in early childhood, and collagen - in adulthood. In adolescence and youthful periods, the highest content of elastin is recorded in the composition of loose connective tissue; this explains the lower tissue density in adolescents and the appearance of joint hypermobility typical of the pubertal period. As a rule, in most patients with CTD over the age of 35, the risk of developing new symptoms is minimal [5,6].

When diagnosing CTD, it is necessary to use the results of clinical, genealogical, laboratory-instrumental, and molecular genetic studies. The clinical examination includes patient history, as well as physical examination, including family members, to confirm the hereditary nature of the disease.

Non-differentiable forms can be diagnosed when the set of phenotypic traits does not fit into any of the known hereditary nosology [1-4]. Unlike monogenic forms, uCTDs do not manifest as acutely and often go unnoticed. Mutations of the genes encoding the synthesis and spatial organization of collagen, which are responsible for the formation of the components of the extracellular matrix and enzymes involved in the processes of fibrillogenesis, have a leading etiological significance [7]; but also make a significant contribution and various exogenous factors, such as - unfavorable environmental conditions, inadequate or irrational nutrition, stress. The main reasons for the formation of connective tissue dysplasia include an abnormal rate of synthesis or folding (assembly) of collagen; synthesis of abnormal collagen and/or elastin; excessive degradation (destruction) of collagen and/or elastin; violations of the structure of collagen and/or elastin fibers due to insufficient cross-linking; tissue destruction through autoimmune reactions and other causes [8-10].

The absence of a unified terminology and generally accepted classification of CTD reflects the disagreement of researchers on this issue. Most often, CTD manifests itself in three main phenotypes: marfanoid, Ehlers-like, and unclassifiable. T. I. Kadurina (2000) distinguishes MASS-phenotype, marfanoid, and Ehlers-like phenotypes. The "Marfanoid phenotype" is characterized by the presence of signs of generalized connective tissue dysplasia with an asthenic physique, dolichostenomelia, arachnodactyly, damage to the valvular apparatus of the heart and aorta, and visual impairment. With an "Ehlers-like phenotype", there is a combination of signs of generalized CTD with a tendency to skin hyper-elasticity and varying degrees of joint hypermobility. The "MASS-like phenotype" is characterized by signs of generalized connective tissue dysplasia, several cardiac disorders, skeletal anomalies, and skin changes in the form of thinning or subatrophy [11,12]. G.I. Nechaeva (2008) [13] proposes to identify clinical syndromes associated with the underlying disease. According to these recommendations, it is customary to distinguish:

1) Dysplastic-dependent changes in organs and systems in CTD (locomotor, skin, visceral);
2) Conditions associated with connective tissue dysplasia; locomotor disorders including deformity of the chest and spine, several pathological changes in the muscular system, osteochondral dysplasia, and other pathologies.

Visceral manifestations include changes in the cardiovascular system (valve prolapse, abnormally located chords, and other anomalies); changes in the respiratory system (polycystic, spontaneous pneumothorax of unknown etiology, tracheobronchial dyskinesia); pathology of the gastrointestinal tract (visceroptosis, anomalies of the gallbladder, dolichosigma); kidney pathology (nephroptosis, developmental anomalies); ophthalmic pathology (myopia, epicanthus, ptosis, progressive pathology of vision).

The pathology of the reproductive system in girls with CTD is also widely covered in Russian scientific research. In two scientific papers on this topic, groups of girls aged 11 to 18 were surveyed. Patients were divided into two groups: the main group consisted of patients with menstrual dysfunction and signs of CTD; the control group included children with menstrual dysfunction without symptoms of CTD [16,17].

The features of the family history, previous diseases, and concomitant somatic and gynecological pathology were taken into account, and the features of the development of menarche were also studied. The peculiarities of gestation and childbirth of their mothers were also considered and anthropometry of the patients was carried out as well [17].

The results showed that pregnancy in mothers with CTD and menstrual dysfunction proceeded to a greater extent with the threat of interruption and, to a lesser extent, with preeclampsia and placental insufficiency [17]. During the assessment of physical development, it was identified that patients with signs of UCTD have disharmonious physical development associated with being underweight. With age, the frequency of occurrence of girls with disharmonious physical development increased [16]. Puberty in girls of the first group was accompanied by low progression rates from the age of 13, proceeded against a hypoestrogenic background, and manifested underdevelopment or weak development of the mammary glands, as well as delayed pubic and axillary hair growth [17,18]. Also in the same group, menstrual dysfunction was characterized by early onset of menarche (at the age of 12 years) [15,17], hypomenstrual syndrome, and uterine bleeding during puberty. The leading symptoms of menstrual dysfunction in girls with CTD are oligomenorrhea (59%), uterine bleeding (22.9%), and secondary amenorrhea (16.4%). Most often, patients of the main group complained of rare, scanty, short menstruation [15,17]. The formation of hypomenstrual syndrome and amenorrhea against the background of UCTD occurs in the second phase of the pubertal period against the background of ovarian hypofunction. Metabolic and hormonal changes cause menstrual dysfunction and exacerbate the course of systemic connective tissue dysplasia [15].

Although the main manifestation is hypomenstrual syndrome, in some of the examined patients, the syndrome of "heavy menstruation" was detected, which is caused by disorders in the primary platelet hemostasis, which is based on the "weakness" of the vascular wall and a decrease in platelet aggregation activity [14]. Activation of the androgen-glucocorticoid function of the adrenal glands in combination with hyperprolactinemia in patients with uCTD leads to anovulatory cycles [24]. In some cases, this category of girls had juvenile bleeding during puberty, which is due to relative hypoestrogenism due to anovulatory cycles [14]. Puberty and the development of menarche in girls with nCTD are accompanied by an increase in the concentration of the luteinizing hormone, and a decrease in the level of estradiol within the reference values [17].

The conducted studies point to the immaturity of the central mechanisms of regulation. An increased release of gonadotropic hormones, especially LH, from puberty can lead to inadequate ovarian stimulation, and dysfunction of the follicular apparatus, which has a risk of developing polycystic ovary syndrome. This is confirmed by the ratio of LH/FSH in the older age group of adolescent girls. In the younger age group, FSH prevails over LH, which indicates the immaturity of the reproductive system. In the symptom complex with AMH (anti-Müllerian hormone) deficiency, these changes in the hormonal profile indicate a delay in sexual development in adolescent girls of both age groups with menstrual irregularities against the background of CDT [25,28].

The size of the uterus in girls with CTD was significantly smaller than in the comparison group. The size of the ovaries in adolescent girls of both groups did not differ statistically. According to an ultrasound of the pelvic organs, 17.6% of adolescent girls with CTD and uterine hypoplasia correlated with being underweight. In more than half of the patients of the main group, an ultrasound revealed certain changes: 15.9% - retrodiction of the uterus, 5.2% - saddle uterus, 4.4% - bicornuate uterus, 25.3% - multi follicular ovarian changes [18].

The psycho-emotional status of girls with CTD with sympathotonia is characterized by higher rates of reactive and personal anxiety, which exacerbates maladaptive and inadequate emotional reactions, including the perception of pain, which is confirmed by a survey of patients, where they note pain during menstruation as acute or severe [14,19]. The loss of adaptive significance, in turn, with an increase in the number and severity of phenotypic signs of CTD, indicates the involvement of a dysplastic background in psychosomatic interactions [20].

Activation of the sympathoadrenal connection leads to remodeling (in the direction of hyperplasia and hypertrophy) of the smooth muscle components of all organs and systems, including in the isthmic-cervical region, which may be one of the causes of dysmenorrhea, followed by the manifestation of another gynecological pathology. Patients with a predominance of the parasympathetic link will subsequently join the group of patients with a hyperemic type of microcirculation - genital prolapse [14].

Dysmenorrhea, according to the International Classification of Diseases of the 10th revision (ICD-10), is painful menstruation without concomitant organic pathology. Taking into account that pain is not the only manifestation of a pathological condition, from the point of view of its impact on the quality of life, from the modern neurophysiological positions, the term "dysmenorrhea" is more appropriate, since it can designate the entire wide range of neurovegetative, metabolic-endocrine and psycho-emotional deviations of the process menstruation [21].

Depending on the pathogenesis, primary and secondary dysmenorrhea are distinguished.

Primary dysmenorrhea is a complex of neurovegetative, metabolic-endocrine, mental, and emotional abnormalities that contribute to the pathological accumulation in the endometrium on the eve and (or) during menstruation of arachidonic acid degradation products (prostaglandins, thromboxanes, leukotrienes, etc.), which enhance the afferentation of impulses and irritation of pain centers (nociception centers) [22].

Secondary dysmenorrhea is caused by the presence of gynecological and (or) endocrine diseases (fibroids, endometriosis, anomalies in the development of the genital organs, inflammatory diseases of the genital organs, pelvic varicose veins, hyperprolactinemia) [22].

In patients with CTD, an important role in the development of pain during menstruation may belong to varicose veins of the small pelvis, scoliosis, instability of various parts of the spine, which, in combination with the syndrome of vegetative-vascular dystonia and asthenic-neurotic syndrome, is essential. The combination of these factors in girls with CTD can reach 79.5% [14].

An important aspect in the genesis of the development of primary dysmenorrhea in girls with CTD is hypomagnesemia. Girls with primary dysmenorrhea are characterized by subclinical magnesium deficiency. There are clear correlations between the level of magnesium in the blood and the intensity of pain, as well as reactive anxiety [14]. Hypomagnesemia leads to a change in the hemodynamics of the small pelvis in the form of hypertension and vasoconstriction, as well as a decrease in the synthesis of opioid neuropeptides in the brain, resulting in a decrease in the threshold of pain sensitivity and the development of a state of chronic stress, which in turn leads to sympathicotonia and the formation of a vicious circle [21].

Clinical manifestations of uCTD and hypomagnesemia, leading to sympathotonia, may be predictors of dysmenorrhea and aggravate the clinical course of menstrual pain syndrome.

Therefore, the treatment of primary dysmenorrhea in girls with CTD should be aimed at correcting autonomic, asthenic-neurotic manifestations and microelement deficiency [14].

According to gynecologists involved in research in the field of connective tissue dysplasia, in case of menstrual dysfunction, treatment with combined estrogen-gestagen drugs in girls with CTD should be refrained, since hormone replacement therapy for violations of the hypothalamic-pituitary functions with unsteady menarche against the background of dysfunction autonomic nervous and thalamocortical systems does not contribute to the proper functioning of the cardiovascular and reproductive systems, especially in dysplastic disorders, including impaired hemostasis [26].

In the case of an irregular menstrual cycle due to a violation of the LH level and the LH/FSH ratio, in the presence of a hyperplastic process in the endometrium with relative hypoestrogenism, it is preferable to use progesterone-based treatments: progesterone, progestogel, utrogestan or a synthetic analog - duphaston [26].

With signs of hypogonadism in adolescent girls, treatment with human chorionic gonadotropin is carried out at an age-appropriate dose of 250 IU to 1500 IU 2 times a week intramuscularly, courses 1 - 2 times a year in the amount of 8 - 10 injections under the control of the hormonal profile (total testosterone, estradiol) [27].

In the absence of effect, as well as anovulatory cycles, ovulation inducers are preferred. With regular menorrhagia, the state of the primary link (vascular-platelet) and coagulation hemostasis should be assessed, and therapy should be directed to the hemostatic aspect during menstruation (rest, tranexamic acid, uterotonic therapy (oxytocin), nettle decoction, calcium preparations, etc.) [14].

In the intermenstrual period, correction of iron deficiency anemia, general strengthening, and vitamin therapy is necessary [14].

Only with severe anemization of the patient, abundant metrorrhagia, and ineffectiveness of hemostatic therapy, it is advisable to consider the issue of hospitalization and hormonal hemostasis with single-phase combined oral contraceptives, followed by the transition to pregnadiene derivatives - 10 days, with further use of the latter in the next three menstrual cycles from 16 to 25 days of the cycle. If there is a violation in the system of the coagulation link, it is advisable to consider the method of plasma transfusion [14].

In the treatment of primary dysmenorrhea, antispasmodics can be prescribed (drotaverine 1 - 2 days before the expected menstruation in combination with NSAIDs in suppository form or systemically (diclofenac). NSAIDs should be prescribed only rectally and if the above therapy is ineffective.

In the treatment of primary dysmenorrhea in girls with CTD, preference should be given to magnesium-based treatments (Magne B6, magnelius, magnesium salt of orotic acid, etc.) [14].

Reactive and personal anxiety, which are the result of activation of the sympathetic nervous system, and autonomic imbalance in combination with the unsteady function of the hypothalamic-pituitary system, expand the indications for the appointment of magnesium preparations.

Magnesium affects the reduction of symptoms of dysmenorrhea and contributes to the prevention of several gynecological diseases in the future (endometriosis, uterine fibroids, etc.) [14].

Progesterone preparations (micro ionized progesterone, progestins) from the 16^{th} to the 25^{th} day of the menstrual cycle are preferable compared to oral contraceptives, but they are more invasive and should have strict indications (pubertal menometrorrhagia, endometrial hyperplastic processes) [14].

It is necessary to take into account the features of the genesis of dysmenorrhea in patients with CTD and assess the emotional spectrum and pain perception before choosing a first-line drug [14].

General strengthening and correcting manifestations of DST are also recommended: correction of the level of free amino acids in the blood (glutamic acid, glycine), correction of disorders in the synthesis and catabolism of glycosaminoglycans (glucosamine sulfate), and chondroprotectors (chondroitin sulfate), which have a chondroprotective and chondrostimulating effect. It is recommended to use chondroprotectors in combination with antioxidants (vitamin C, vitamin E, and beta-carotene) [14].

Non-drug therapy is also recommended: a complex of physiotherapy exercises, therapeutic massage, swimming, psychological correction, physiotherapy, and diet therapy [14,23].

Conclusion

In conclusion, it can be summarized that adolescent girls with the peculiarities of connective tissue structure - the presence of mesenchymal pathology - nCDT are more likely to have disorders of menarche formation, abnormal development and functioning of reproductive system organs, deviations in the timing of puberty, appearance of secondary sexual characteristics, deviations in the hormonal profile. This polymorphism of clinical symptoms of nCDT associated with the reproductive system can be corrected by medication at the stage of manifestation.

Bibliography

1. Connective tissue dysplasia. Clinical guidelines RNMOT. M: RNMOT (2017): 181.
2. VM Yakovlev. "Connective tissue dysplasia in the practice of primary care physicians". Guide for doctors-M.: KST Interforum (2016): 520.
3. NB Pashinskaya., *et al*. "Structure, and frequency of occurrence of various syndromes of connective tissue dysplasia in somatic pathology in children and adolescents". Pediatric aspects of connective tissue dysplasia. Achievements and prospects: Russian collection of scientific papers with international participation (2013): 37-39.
4. AV Goryainova., *et al*. "The role of undifferentiated connective tissue dysplasia during cystic fibrosis in children Actual problems of abdominal pathology in children". Proceedings of the XXV Congress of Pediatric Gastroenterologists in Russia and CIS countries. M.: Publishing House "Medpraktika-M" (2018): 245-249.
5. "The Role of Connective Tissue Dysplasia During Cystic Fibrisis in Children: Clinical And Genetic Markers". Abstract of the dissertation for the degree of Candidate of Medical Sciences (2019): 3.
6. NB Pashinskaya., *et al*. "Structure and frequency of occurrence of various syndromes of connective tissue dysplasia in somatic pathology in children and adolescents". Pediatric aspects of connective tissue dysplasia. Achievements and prospects: Russian collection of scientific papers with international participation (2013): 37-39.
7. Burrows NP. "The molecular genetics of the Ehlers-Danlos syndrome". *Clinical and Experimental Dermatology* 24.2 (1999): 99-106.
8. KE Kadler., *et al*. "Collagens at a glance". *Journal of Cell Science* 120.12 (2007): 1955-1958.
9. YP Han. "Essential role of matrix metalloproteinases in interleukin-1-induced myofibroblastic activation of hepatic stellate cell in collagen". *Journal of Biological Chemistry* 279.6 (2004): 4820-4828.
10. Kadler KE. "Collagen fibrillogenesis: fibronectin, integrins, and minor collagens as organizers and nucleators". *Current Opinion in Cell Biology* 20.5 (2008): 495-501.
11. Kadurina TI and VN Gorbunov. "Connective tissue dysplasia: a guide for physicians". St. Petersburg: Elbi (2009): 714.
12. Kadurina TI and LN Abbakumova. "Pediatric aspects of the diagnosis of joint hypermobility syndrome". *Pediatrics* 92.4 (2013): 46-51.
13. GI Nechaev., *et al*. Connective tissue dysplasia: main clinical syndromes, diagnosis, treatment". *Attending Physician* 1 (2008): 24-34.
14. AI Martynov., *et al*. National recommendations of the Russian scientific medical society of therapists for the diagnosis, treatment, and rehabilitation of patients with connective tissue dysplasia Medical Bulletin of the North Caucasus 11.1 (2016): 2-76.
15. EV Zoloto. "Predictors of reproductive health disorders in adolescent girls with undifferentiated connective tissue dysplasia". *Archive of Clinical and Experimental Medicine* 28.2 (2019): 160-167.
16. OV Trushina., *et al*. "Physical development and somatic background of adolescent girls suffering from dysmenorrhea combined with connective tissue dysplasia". Scientific Bulletin of the Belgorod State University. Series: Medicine. Pharmacy 41.1 (2018): 36-45.
17. EA Stepanova and SI Kolesnikov. "Menstrual disorders in adolescent girls with connective tissue dysplasia". *Bulletin of the East Siberian Scientific Center of the Siberian Branch of the Russian Academy of Medical Sciences* 2.84 (2012): 49-53.

18. GA Skosyreva., *et al*. "Formation of reproductive health of adolescent girls with undifferentiated connective tissue dysplasia syndrome". *Kazan Medical Journal* 88.5 (2007): 120-122.

19. VS Orlova., *et al*. "Connective tissue dysplasia is a factor that exacerbates menstrual pain in adolescence". *Journal of Obstetrics and Women's Diseases* 67.1 (2018): 38-46.

20. GI Nechaeva and IV Druk. "Psychosomatic ratios in connective tissue dysplasia". *Siberian Bulletin of Psychiatry and Narcology* 3.37 (2005): 78-80.

21. AP Gevorgyan., *et al*. Primary dysmenorrhea in adolescent girls as a predictor of the development of undifferentiated connective tissue dysplasia Problems of reproduction 23.3 (2017): 77-85.

22. OI Gumenyuk and YV Chernenkov. "Dysmenorrhea in adolescent girls". *Nuse* 3 (2015): 31-33.

23. EG Yurova., *et al*. "Rehabilitation of adolescent girls with impaired reproductive function associated with connective tissue dysplasia in the children's sanatorium "Belokurikha". *Kuban Scientific Medical Bulletin* 6 (2009): 83-86.

24. TL Smirnova and LI Gerasimova. "Features of clinical manifestations of the syndrome of undifferentiated connective tissue dysplasia". Doctor. RU 8.152 (2018): 40-44.

25. EV Zoloto. "Features of the hormonal status of adolescent girls with menstrual irregularities against the background of undifferentiated connective tissue dysplasia". *Medico-social problems of the family* 24.1 (2019): 23-27.

26. VA Kucherov., *et al*. "Possibilities of treating connective tissue dysplasia in children and adolescents". *Ural Medical Journal* 2 (2019): 20-25.

27. YA Kravtsov., *et al*. Applicant State budgetary educational institution of higher professional education "Pacific State Medical University" of the Ministry of Health of the Russian Federation (GBOU VPO TSMU M) (2016).

28. AV Goryainova., *et al*. "Features of sexual development of adolescent girls with cystic fibrosis". *Russian Pediatric Journal* 25.4 (2022): 230-235.

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