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The Relationship of Changes in the State of Connective Tissue and Hypomagnesemia in Juvenile Dysmenorrhea

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According to WHO, the prevalence of menstrual pain syndrome in the structure of adolescent gynecological pathology is extremely high, while about 15% of them characterize menstrual pain as excruciating [5]. Juvenile dysmenorrhea –JD) - painful menstruation in girls under 18 years of age in the absence of pelvic pathology is a common and often debilitating gynecological suffering regardless of age or nationality [2,4]. Despite the high prevalence, primary dysmenorrhea in girls is often poorly diagnosed and even ignored by medical professionals and by the girls themselves and their mothers, who may accept painful menstruation as a normal part of the menstrual cycle[1,3]. In the publications of a number of researchers, dysmenorrhea is listed among many manifestations of connective tissue dysmorphic disorder [6]. The main component of connective tissue is collagen fibers, and oxyproline is a biochemical marker of its decay [13]. Magnesium occupies a special place among the leading macro- and microelements involved in collagen biosynthesis.

THE AIM of the STYDY was to identify the relationship between hypomagnesemia and connective tissue diplasia (CTD) in girls suffering from primary dysmenorrhea.

RESEARCH MATERIAL AND METHODS: the data obtained during the examination, observation, treatment, and management of 230 girls with primary dysmenorrhea aged 12 to 17 years, 11 months and 29 days with and without signs of CTD were analyzed. The main group was divided into 3 groups depending on the severity of the pain syndrome on the severity of dysmenorrhea, which was carried out using a visual-analog pain scale. 50 practically healthy girls with a normal menstrual cycle were.

Examination of girls with juvenile dysmenorrhea to identify CTD criteria was carried out according to the following parameters: 1) a clinical interview, during which the general state of health, heredity, allergoanamnesis, previous diseases were clarified. 2) Phenotypic signs and severity of CTD were assessed using a diagnostic table developed by T. I. Kadurina (2008) [8], which were detected anamnetically, inclyding during physical examination, or by routine instrumental diagnostics methods, without resorting to high-tech research methods (Table 1).

Table 1

Phenotypic manifestations of CTD in points

Sign	Points	+/-
Asthenic type of constitution, body weight deficit	1	
Hyperelastic skin: mild grade	2	
Expressed	3	

Keloid scars	2	
Atrophic striae	2	
Hemorrhagic syndrome	2	
Joint hypermobility: mild	2	
Expressed	3	
Flat feet	2	
Thin skin	2	
Blue sclera	1	
Thin hair	2	
Brittle nails	1	
Soft auricles	2	
Paradontitis	1	
Teething anomalies	2	
Dolichostenomelia	3	
Asymmetry of the shoulder blades	2	
Myopia: mild	1	
severe degree	2	
Arterial hypotension	1	
Gastrointestinal dysfunction	2	
Vegetative vascular dysfunction	3	
Tendency to allergic reactions	2	

Each feature was assigned a diagnostic value (in points). According to the sum of the points, the conclusion was given: the sum of points less than 9 – mild severity (mild), from 9 to 14 - moderate severity (moderate), from 15 and more - severe severity (pronounced).

The distribution of the surveyed girls with JD with CTD according to the score evaluation criteria is presented in Table 2.

Table 2
Distribution of the surveyed with JD with CTD according
to the score evaluation criteria

Severity of juvenile dysmenorrhea	Score evaluation of CTD criteria					
	Up to 9 points		9-14 points		Over 15 points	
	n=85	%	n=57	%	n=32	%
Mild severity n=17	11	6,3	5	2,8	1	0,6
Medium-heavy n=89	45	25,8	31	17,8	13	7,4
Severe degree n=68	29	16,6	21	12,06	18	10,3

In girls with JD with the presence of CTD criteria, 11 (6.3%) had phenotypic signs up to 9 points with mild severity, 45 (25.8%) with moderate severity, and only 29 (16.6%) with severe JD. Moderate severity criteria were found in 5 (2.8%) with mild, in 31 (17.8%) with moderate severity and in 21 (12.06%) with severe ED. Phenotypic signs corresponding to the expressed criteria of CTD were found in only 32 girls, which, in percentage terms, were 0,6%,7,4%,10,3%. Consequently, with the aggravation of the severity of dysmenorrhea, the criteria of CTD are increasingly manifested. In the contingent prevailed girl with the presence of criteria of CTD, the number was 174 (75,6%). Determination of free and bound hydroxyproline in urine is carried out according to the method Sharaev P. N.[13], determination of magnesium (Mg) in serum was carried out on the device the spectrofluorimeter type REF 610 A RAYLEIGH LTD Shanghei ANTAI Diagnosties Co., LTD.) using sets of test systems HUMAN (Elisa). The data obtained during the stydy were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2012 software package, inclyding the use of built-in statistical processing functions.

THE RESULTS OBTAINED AND THEIR DISCUSSION In girls with juvenile dysmenorrhea without CTD, regardless of its severity, we did not detect changes in the content of free peptide-bound and protein-bound oxyproline. The

absolute values in the groups did not differ significantly from the indicators of practically healthy girls. In the group of girls with JD and signs of CTD, we revealed a progressive increase in the excretion of free and peptide-bound oxyproline in the urine, depending on the severity of dysmenorrhea, and the content of protein-bound oxyproline did not change significantly. Thus, in girls with the presence of CTD manifestations with mild dysmenorrhea, the content of free and peptide-bound oxyproline in the urine increased statistically significantly by 1.41 (P<0.001); 1.06 (P<0.01) times, respectively, relative to the values of the group of girls with JD without CTD; 1.38 (P<0.001); 1.05 (P<0.01) times, respectively, relative to the values of the group of practically healthy girls.

Table 3

The level of oxyproline in daily urine (mmol / day) in girls with primary dysmenorrhea, depending on the presence of CTD criteria, M ± m

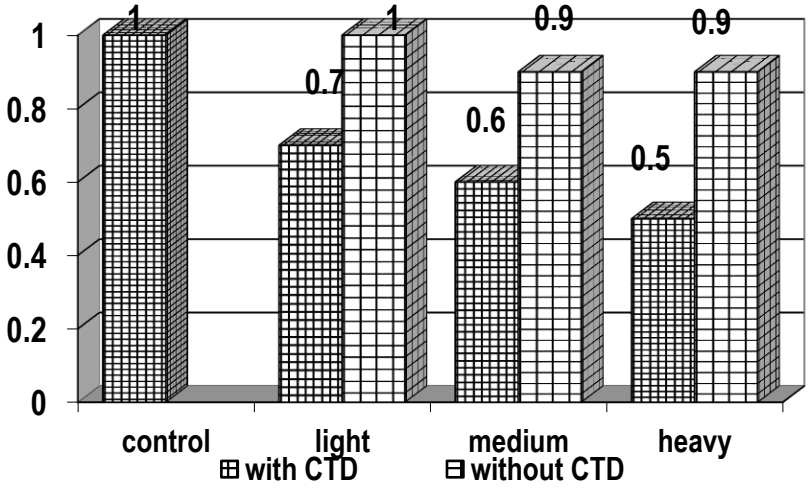
Groups	Oxyproline content, mkmol/day		
	Free	Peptide-bound	Protein-bound
Practically healthy, n=25	18,4±1,34	155,7±13,6	8,4±0,63
JD without CTD			
light, n=10,	18,81±0,30	156,63±0,16	8,33±0,26
medium, n=31	18,42±0,27	155,81±0,24	8,32±0,23
heavy, n=15	17,82±0,35	156,33±0,37	8,11±0,35
JD with CTD			
light, n=24	26,02±0,96[a,б]	163,64±0,97[a,б]	8,45±0,55
medium,n=100	34,54±1,07[a,б]	167,33±0,92[a,б]	8,20±0,63
heavy, n=50	57,83±0,88[a,б]	171,06±0,97[a,б]	8,82±1,51

Note: a - differences with respect to the data of the group of healthy girls are significant, b - differences with respect to the data of the group of girls with JD without CTD are significant (P<0.05).

In girls with moderate JD and with the presence of manifestations of CTD, the content of free and peptide-bound oxyproline in the urine was 1.87 (P<0.001); 1.07 (P<0.05) times higher than in the group of practically healthy girls; 1.87 (P<0.001); 1.07 (P<0.05) than in the group of girls with JD without the manifestation of CTD. In severe JD, a more pronounced increase in the content of free and peptide-bound oxyproline was found in girls with signs of CTD. Their values increased by 3.14 (P<0.001); 1.09 (P<0.05), than in the girls of the control group; 3.24 (P<0.001); 1.09 (P<0.05) times, than in the group of girls without CTD. According to Trushina O.V. et al. (2018), the risk group for severe primary dysmenorrhea is adolescent girls with signs of undifferentiated CTD [12]. Correlation analysis between oxyproline excretion and the degree of JD showed a strong positive correlation between the content of free oxyproline and the severity of dysmenorrhea (r=+0.86±0.25, p<0.02).

Consequently, the more severe the degree of dysmenorrhea in girls with CTD, the higher the indicators of free oxyproline, and in girls without CTD, the indicators of oxyproline did not change significantly. The more criteria for CTD in girls with dysmenorrhea, the higher the severity of dysmenorrhea and the more they show increased urinary excretion of oxyproline, which is confirmed by the presence of a strong positive correlation. Based on the data obtained, it can be said that by stydying the content of oxyproline and oxyproline-containing proteins, it is possible to obtain information about the state of the connective tissue matrix of the affected organ. The detection of an increased level of free oxyproline in the daily urine is an indicator of increased collagen breakdown in the body. One of the manifestations of CTD is a deficiency of an essential macronutrient - magnesium. The method for determining magnesium in blood serum had sensitivity =95.2%, specificity=98%, PPV=99.5%, NPV=81.6%.

Results of the stydy of magnesium content in blood serum of girls with primary dysmenorrhea is shown in Figure 1.



As can be seen from the presented material, the magnesium content in the blood in the group of girls with JD without the manifestation of CTD only tended to decrease, amounting to 1,061± 0.023; 0.913± 0.032 and 0.902± 0.031 mmol/l, respectively, the severity of dysmenorrhea – mild, moderate and severe, with the value of this indicator in the group of practically healthy girls 1,077± 0.003 mmol/l. In the group of girls with mild JD and with the presence of manifestations of CTD, the content of magnesium in the blood serum was 0.712±0.039 mmol/l, which was significantly lower at 1.49 ($P<0.032$) and 1.51 ($P<0.032$) times more than in the group of girls with JD without CTD and practically healthy, respectively. In the group of girls with moderate JD and with the presence of CTD, the magnesium content in the blood serum was 0.621±0.027 mmol/l, which was significantly lower by 1.47 ($P<0.032$) and 1.73 ($P<0.032$) times than in the group of girls with JD without CTD and practically healthy, In the group of girls with severe JD with signs of CTD, a more pronounced decrease in serum magnesium content was found: a decrease to 0.517±0.026 mmol/l, which was significantly lower by 1.74 ($P<0.032$) and 2.08 ($P<0.032$) times than in the group of girls with JD without CTD and practically healthy, respectively. Correlation analysis showed a strong inverse correlation between the content of free oxyproline and magnesium content ($r=-0.89±0.2$, $p<0.01$) and a strong inverse correlation between the severity of dysmenorrhea and magnesium content ($r=-0.98±0.1$, $p<0.01$).

Consequently, girls suffering from primary dysmenorrhea of varying degrees and having signs of CTD had hypomagnesemia, which was dependent on the severity of dysmenorrhea and the presence of CTD. The stydy of the relationship between the content of free oxyproline in daily urine and the level of magnesium in blood serum showed a noticeable increase in the excretion of free oxyproline, against the background of a significant decrease in the content of magnesium in blood serum. This indicated an increased breakdown of collagen, which is an integral part of the connective tissue covering the pelvic organs and part of the ligamentous apparatus of the uterus. It is believed that magnesium indirectly affects the synthesis of collagen through its effect on the higher vegetative center – the hypothalamus and participates in the synthesis of a number of neuropeptides of the brain. To date, magnesium deficiency occupies a leading position among the pathology of the elemental status, and according to ICD-10, the diagnosis of "Magnesium deficiency" is encoded as E61.2.

A large number of stydies have been devoted to the problem of magnesium deficiency, according to researchers from Italy, it can play an important role in several clinical conditions concerning women's health, where dysmenorrhea is indicated [20]. The lack of magnesium and pyridoxine leads to hypertension and vascular spasm or prolonged vasodilation and venous stagnation, which leads to a change in the hemodynamics of the pelvis, which is caused by an increase in the concentration of prostaglandins in the body. This, in turn, contributes to cell hypoxia, the accumulation of algogenic substances with irritation of nerve endings and the occurrence of pain in the lower abdomen. With a lack of magnesium, a violation of the formation of connective tissue in the form of its undifferentiated dysplasia was often noted. The condition of chronic stress in adolescents leads to significant losses of magnesium in the urine, while absorption in the gastrointestinal tract is significantly reduced, which ultimately leads to a violation of collagen production in connective tissue.

Thus, based on the above, it can be assumed that primary dysmenorrhea can indeed be attributed to a number of manifestations of connective tissue dysmorphic disorder, which is often the result of magnesium deficiency, most often of an innate nature. The presence of CTD criteria in girls with JD suggests the prescription of the process of destruction of collagen fibers and disorders of collagen formation associated with magnesium deficiency since the formation and functioning of the reproductive system of the female body.

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