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Juvenile Dysmenorrhea as a Genetically Determined Condition in the Presence of Criteria of Undifferentiated Connective Tissue Dysplasia in Uzbek Women

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ABSTRACT

The aim of the study was to identify the COL1A1 and G2046T genes in the presence of criteria for undifferentiated connective tissue dysplasia in Uzbek women with juvenile dysmenorrhea. A clinical examination of 230 girls, with signs of CTD -136 and without it-56, the control group consisted of 50 healthy girls with normal menstruation, and a genetic examination of 118 girls aged 13 to 18 years, with signs of CTD-64 and without it-54, the control group consisted of 68 healthy girls with normal menstruation. Determination of free and bound oxyproline in urine was carried out according to the P.N. Sharaev's method. It is revealed that with the aggravation of the severity of dysmenorrhea, the criteria for CTD are increasingly manifested. The study of the association of the COL1A1 G2046T genotype revealed a significant increase in the mutant TT genotype in the group of girls with JD with CTD, compared with practically healthy individuals. Analysis of the distribution of allelic variants of the COL1A1 G2046T gene showed that in the group of patients with DM accompanied by CTD significantly higher than in the control group of practically healthy individuals, there was only a tendency to the reliability of alleles, but they did not reach true significance. Correlation analysis between the excretion of oxyproline and the degree of UD showed a strong positive correlation between the content of free oxyproline and the severity of dysmenorrhea ($r=+0.86\pm0.25$, $p<0.02$). In the group of girls with JD and CTD compared to the control group ($\chi2=4,302$, $p<0.03$, $OR\geq4.71$), a significant increase in the homozygous TT genotype was noted. The presence of COL1A1 and G2046T genes in the presence of criteria for undifferentiated connective tissue dysplasia in Uzbek women is a risk factor for the development of juvenile dysmenorrhea.

KEY WORDS: juvenile dysmenorrhea, connective tissue dysplasia, oxyproline, quality of life.

INTRODUCTION

Pain syndrome that accompanies the physiological process-menstruation is considered worldwide as one of the factors that worsen the quality of life of girls and adolescent girls [13, 22, 26]. According to the WHO, in the structure of adolescent gynecological pathology, the prevalence of menstrual pain is extremely high, with about 15% of them describing menstrual pain as excruciating [1, 2, 21, 23]. In girls under 18 years of age in the absence of pelvic pathology, juvenile dysmenorrhea (JD) – painful menstruation is a common and often debilitating gynecological suffering, which does not depend on age or nationality at all [15,19,25]. At least primary dysmenorrhea in girls is highly common, but it is often poorly diagnosed and even ignored by medical professionals and by the girls themselves and their mothers, who consider painful menstruation as a normal phenomenon of the menstrual cycle [7,18,20]. Along with the fact that juvenile dysmenorrhea (JD) is a signal of disorders that have

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developed in the systems that provide and control the process of endometrial rejection, this issue requires an urgent solution [4]. When a pathological situation occurs in the body of a growing female organism, the formation of pathological conditions of organs and tissues occurs in the form of undifferentiated connective tissue dysplasia h (DST) [6,12]. The main component of connective tissue is collagen fibers, and oxyproline is a biochemical marker of its breakdown [5]. The connective tissue is continuously renewed, undergoing rearrangement in response to stress and damage. The intensity of collagen biosynthesis by fibroblasts depends on many factors: hereditary, hormonal, and metabolic [9]. When studying DST and its undifferentiated manifestations in girls with UD, the question arises about the possible cause of changes in connective tissue based on genetic predisposition. As you know, the manifestation of a particular disease is often caused by a combination of certain allelic variants of genes in the genotype of the growing organism, polymorphisms that form a certain hereditary background, which can be realized when the pathological genotype interacts with environmental factors. A number of studies have found some hypotheses listed below, which are still relevant to this day. These studies revealed morphological changes characteristic of nDST and changes in the genes encoding the synthesis and spatial organization of collagen, as well as gene defects of enzymes, cofactors, and steroid hormones, leading to changes in the architectonics of connective tissue. The influence of the environment plays the role of starting factors [10, 16].

To date, it is known that collagens are one of the most abundant proteins in the extracellular matrix and in connective tissue, which differ in their position in the tissue and in the function they carry. There are four main types of collagen (I–IV), which include the following genes: collagen I (genes COL1A1, COL1A2) – the main component of bone, which is also present in scars, tendons and cartilage; collagen II (gene COL2A1) - the main component of cartilage; collagen III (gene COL3A1) forms the reticular fibers that hold together the extracellular matrix; collagen IV (genes COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6) forms the basal lamina on which the epithelium is held. [11, 24]. It was found that in women with systemic connective tissue insufficiency, there is a partial decrease in type I collagen in the interstitial substance, which is probably a consequence of impaired collagen secretion during its preserved synthesis [17]. Some studies revealed that all patients with a DST regardless of the severity of collagen type I and III was atypical of the spatial structure, without the formation of bundles of fibers expressed and then replaced in the ligaments of collagen I and III, collagen type IV, leading to profound disturbances of the mechanical characteristics and functionalfailure of the design-ligamentous supporting tissues of the pelvis [8].

There is an opinion that in the presence of a genetic predisposition in the future, especially with the adverse effects of external factors, certain clinical forms of the disease are observed. In order to detect this genetic predisposition, a number of scientists have studied the polymorphism of the type I collagen receptor gene (COL1A1). The type I collagen (COL1A1) alpha chain gene is located on chromosome 17q21. 3-22. The G2046T polymorphism is a point substitution of G at TV position 2046, localized in the non-coding region of the gene affecting the binding site of the transcription factor of the alpha-1 gene of the type 1 collagen chain.

Considering DST as a result of a defect in the genes of collagens, much attention is paid in the literature to the components responsible for the metabolism of the latter: fibrillogenesis proteins, cross-links responsible for the ordered distribution of collagen chains and its

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remodeling (degradation and proteolysis)[3].To date, morphological changes characteristic of DST and changes in the genes encoding the synthesis and spatial organization of collagen, as well as gene defects of enzymes, cofactors and steroid hormones leading to changes in the architectonics of connective tissue have been identified [8,11,24].

The aim of the study was to identify the COL1A1 and G2046T genes in the presence of criteria for undifferentiated connective tissue dysplasia in Uzbek women with juvenile dysmenorrhea.

MATERIALS AND METHODS

A clinical examination of 230 girls with signs of DST -136 and without it-56, the control group consisted of 50 healthy girls with normal menstruation, and a genetic examination of 118 girls aged 13 to 18 years, with signs of DST-64 and without it-54, the control group consisted of 68 healthy girls with normal menstruation. The genetic study was carried out by polymerase chain reaction (PCR) using specific primers (NPF Litech, Russia) in an automatic amplifier "RotorGeene 6000". The determination of free and bound oxyproline in the urine was carried out according to the method of Sharaev P. N. [14]. The data obtained during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2012 software package.

RESULTS

The reason for the diagnosis of dysmenorrhea was a complaint about painful menstruation. They had a single instant health examination to exclude organic pathology, i.e. secondary dysmenorrhea (ultrasound of the pelvic organs, smear on the flora, examination by a vertebrologist). The patients were divided into 3 groups depending on the severity of mild UD in 34 (14.7%), moderate in 131 (56.9%), and severe dysmenorrhea in 65 (28.3%). In each of the three groups, two groups were identified according to the presence of DST signs in the patients. It should be noted that patients with severe manifestations of DST were not found in our study. Since the publications of a number of researchers list dysmenorrhea as one of the many manifestations of DST, we conducted a survey of girls with juvenile dysmenorrhea with the identification of DST criteria for the following parameters: 1) a clinical interview, during which the general state of health, heredity, allergoanamnesis, and previous diseases were clarified. 2) The phenotypic features and severity of DST were evaluated using a diagnostic table developed by T. I. Kadurina (2008) [3], which were identified anamnetically, including during physical examination, or by routine instrumental diagnostics, without resorting to high-tech research methods (Table 1). Each feature was assigned a diagnostic value (in points). By the sum of points given conclusion: a score of less than 9 – light severity (low), from 9 to 14 – moderate severity (moderately severe), from 15 and above – severe degree (severe).

In girls with UD with the presence of DST criteria, 11 (6.3%) had phenotypic signs up to 9points, 45(25.8%) had moderate severity, and only 29 (16.6%) had severe UD.

Table 1. Instrumental diagnostics, without the use of high-tech research methods.

Flag	The Points	+/- Attribute

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Asthenic type of Constitution, body mass deficit	1	
Hyperelastic skin: mild grade	2	
Expressed	3	
Kelloid scars	2	
Atrophic striae	2	
Hemorrhagic syndrome	2	
Hypermobility Joint hypermobility: mild	2	
Expressed	3	
Flat	feet 2	
Thin skin	2	
Blue sclera	1	
Thin hair	2	
Brittle nails	1	
Soft auricles	2	
Paradontit	1	
Teething anomalies	2	
Dolichostenomelia	3	
Shoulder blade asymmetry	2	
Myopia: mild grade	1	
severe grade	2	
Arterial hypotension	1	
Git dysfunction	2	
Vegetative vascular dysfunction	3	
Tendency to allergic reactions	2	

Moderate severity criteria were found in 5 (2.8%) with mild, in 31 (17.8%) with moderate-severe, and in 21(12.06%) with severe DM (Table 2). Phenotypic signs corresponding to the expressed criteria of DST were found in only 32 girls, which in percentage ratio were respectively 0,6%,7,4%,10,3%. Consequently, with the aggravation of the severity of dysmenorrhea, the criteria of DST are increasingly manifested. The examined patients were consulted by a general practitioner, an optometrist, an otolaryngologist, and a dentist.

Identification of DST criteria in the girls of the survey group and the main group had sensitivity-72.8 and 70.8%, specificity-92 and 92%. In the survey group, the positive prognostic value was 96.2%, and the negative prognostic value was 54.7%, and in the main group – 97.6 and 54.7%, respectively.

Table 2. Distribution of the examined children with JD with DST accordingto the score of criteria

Degree of severity of juvenile dysmenorrhea	Scoring criteria for DST					
	Up to 9 points		9-14 points		Over 15 points	
	n=84	%	n=58	%	n=33	%
Mild severity n=17	11	6.3	5	2.8	1	0.6

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Moderate-severe n=89	45	25.8	31	17.8	13	7.4
Severe n=68	29	16.6	21	12.06	18	10.3

The distribution of those surveyed according to the availability of DST criteria is shown in table. 3.

Table 3. Distribution of respondents by availability of DST criteria.

The handles DST	Main group	
	n=230	%
body mass Deficit	143	62.1*
Muscle hypotension	139	60.4
Flattening of the arch of the foot	103	44.7**
Tendency to light bruising	121	52.6
Vegetative vascular dysfunctions	146	63.4
spinal Deformity (scoliosis, kyphosis, kyphoscoliosis)	104	45.2**
Hyper-mobility of joints, tendency to dislocations, sprains of the ligamentous apparatus	94	40.8
Tendency to allergic reactions	139	60.4
Tendency to colds	137	59.5
History of tonsillectomy	36	15.6
Violation of the evacuation function of the gastrointestinal tract	52	22.6
Myopia of varying degrees	73	31.7

Note: * - differences on the data guppy healthy girls significant, ** – differences on the data of the group of girls with a YUD without DST significant (P<0,05).

As shown in Table 5, the analysis of the distribution of allelic variants of the COL1A1 G2046T gene showed that in the group of patients with UD accompanied by DST significantly higher than in the control group of practically healthy individuals, there was only a tendency to the reliability of alleles, but they did not achieve true significance.

Table 5. Distribution of frequencies of alleles and genotypes of the COL1A1 G2046T gene ingirls with UD with DST compared to the control group of practically healthy individuals

Genotype	of JD+DST		Control		OR	OR22	P
	n=64	%	n=68	%			
G	97	75.78	114	83.82	0.60	2.658	0.1
T	31	24.22	22	16.18	1.66	2.658	0.1
GG	41	64.06	48	70.59	0.74	0.639	0.4
GT	15	23.44	18	26.47	0.85	0.162	0.6
TT	8	12.50	2	2.94	4.71	4.302	0.03

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Whereas a significant increase in the homozygous TT genotype was observed in the group of girls with JD and DST compared to the control group ($\chi 2 = 4.302$, $p < 0.03$, OR≥4.71). Further, when studying the distribution of allelic variants of the COL1A1 G2046T gene in the group of patients with UD accompanied by DST compared to the group of girls with UD without DST, it was found that there were no significant differences in the frequencies of alleles in these groups (Table 6).

At the next stage, it was decided to analyze the frequency distribution of allelic variants and genotypes of COL1A1 G2046T in the group of girls with UD without DST compared to practically healthy individuals in the population control.

Table 6. Frequency distribution of alleles and genotypes of the COL1A1 G2046T gene in girlswith UD with DST compared to the control group with UD without DST

Genotype	JD+DST		JD without DST		OR	$\chi 2$	P
	n=64	%	n=54	%			
G	97	75.78	88	81.48	0.71	1.124	0.2
T	31	24.22	20	18.52	1.41	1.124	0.2
GG	41	64.06	37	68.52	0.82	0.26	0.6
GT	15	23.44	14	25.93	0.87	0.09	0.7
TT	8	12.50	3	5.56	2.43	1.671	0.2

As can be seen from table 7, during the analysis of these groups, no significant difference was found either for allelic variants or for genotypes.

Table 7. Frequency distribution of alleles and genotypes of the COL1A1 G2046T gene in girlswith JD without DST in comparison with the control group of practically healthy individuals.

Genotype	of JD without DST		Control		OR	OR22	P
	n=54	%	n=68	%			
G	88	66.67	114	83.82	0.85	0.23	0.6
T	20	18.52	22	16.18	1.18		
GG	37	68.52	48	70.59	0.91	0.06	0.8
GT	14	25.93	18	26.47	0.97	0.005	1
TT	3	5.56	2	2.94	1.94	0.523	0.4

Thus, when studying the Association of the COL1A1 G2046T genotype, a significant increase in the mutant TT genotype was revealed TT in the group of girls with JD with DST, compared with practically healthy individuals.

Determination of the content of oxyproline in the urine provides information about the state of metabolism of the main connective tissue protein-collagen in diseases that are accompanied by destructive processes in the connective tissue. As can be seen from table 8, we did not detect any changes in the content of free peptide-bound and protein-bound oxyproline in girls with juvenile dysmenorrhea without DST, regardless of its severity.

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Table 8. Oxyproline level in daily urine (mmol/day) in girls with JD depending on theavailability of DST criteria, M±m.

Groups	The contents of hJ Droxyproline, mmol/day		
	With nobody	Peptide-bound	Protein-bound
Healthy, n=25	18,4±1,34	155,7±13,6	8,4±0,63
YUD without DST			
light, n=10	18,81±0,30	156,63±0,16	8,33±0,26
average, n=31	18,42±0,27	155,81±0,24	8,32±0,23
severe, n=15	17,82±0,35	156,33±0,37	8,11±0,35
YUD with DST			
light, n=24	26,02±0,96[and,b]	163,64±0,97[andb]	of 8.45±0,55
average, n=100	34,54±1,07[a,b]	167,33±0,92[a,b]	8,20±0,63
heavy n=50	of 57.83±0,88[a,b]	171,06±0,97[andb]	of 8.82±1,51

Note: a-differences relative to the data of the group of healthy girls are significant, b-differences relative to the data of the group of girls with JD without DST are significant (P<0,05).

The absolute values in the groups did not differ significantly from the indicators of practically healthy girls. In the group of girls with UD and signs of DST, we found 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 DST manifestations in mild dysmenorrhea, the content of free and peptide-bound oxyproline in the urine significantly increased by 1.41 (P<0.001); 1.06 (P<0.01) times, respectively, relative to the values of the group of girls with UD without DST manifestations; 1.38 (P<0.001); 1.05 (P<0.01) times, respectively, relative to the values of the group of practically healthy girls.

In girls with moderate juvenile dysmenorrhea and with the presence of DST manifestations, 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 UD without DST manifestations.

In severe dysmenorrhea, a more pronounced increase in the content of free and peptide-bound oxyproline was found in young women with signs of DST. Their values increased 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 of JD without DST.

DISCUSSION

Correlation analysis between oxyproline excretion and the degree of UD showed a strong positive correlation between the content of free oxyproline and the severity of dysmenorrhea (r=+0.86±0.25, p<0.02). This may suggest that the single-nucleotide variant COL1A1 G2046T, plays a role in the pathogenesis of the development of UD, accompanied by DST. This is indirectly confirmed by the indicators of oxyproline (Table. 8), but taking into account the fact that the increase in the level of this indicator was significant both in

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comparison with practically healthy individuals and in comparison with a group of patients with UD without signs of DST, it allows us to assume that this polymorphism is only one of the polymorphisms involved in the pathogenesis of the studied pathology. The presence of the COL1A1 and G2046T genes in the presence of criteria for undifferentiated connective tissue dysplasia in Uzbek women is a risk factor for the development of juvenile dysmenorrhea.

Consequently, the more severe the degree of dysmenorrhea in girls with DST, the higher the indicators of free oxyproline, and in girls without DST, the indicators of oxyproline did not change significantly.

The more criteria for DST 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 studying 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. Detection of high levels of free hJDroxyproline in daily urine is an indicator of enhanced collagen breakdown in the body, and the girls with the presence of manifestations of DST for YUD worse.

CONCLUSION

The detectability of oxyprolinuria in girls with pDST in juvenile dysmenorrhea indicates a violation of the state of collagen in the connective tissue that is part of the ligaments of the pelvic organs.

The occurrence of the mutant allele of the estrogen – alpha receptor gene (single-nucleotide substitution of guanine for adenine in rs2228480) is 1.9 times higher in the group of girls with DST and DD than in the group of DD without DST ($\chi 2 = 4.515$; $p=0.03$).

The girls with a YUD with a DST discovered a significant difference in the frequency of gene polymorphism of collagen type I (single-nucleotide replacement of guanine to thymine in rs1800012) in comparison with group of practically healthy individuals ($\chi 2=4,71$; $p = 0.03$).

In the group of girls with a YUD and DST compared to the control group ($\chi 2=4,302$, $p<0,03$, $OR\geq 4,71$) showed a significant increase of the homozygous genotype TT. The presence of the COL1A1 and G2046T genes in the presence of criteria for undifferentiated connective tissue dysplasia in Uzbek women is a risk factor for the development of juvenile dysmenorrhea.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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