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ASSOCIATION OF SPINE DEFORMATION PROGRESSION IN CHILDREN WITH IDIOPATHIC SCOLIOSIS AND FOLATE CYCLE GENE POLYMORPHISM

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Background. One of the most common orthopedic pathologies in children aged 10–18 years is idiopathic scoliosis, which is diagnosed in 2%–3% of cases in the general population.
Aim. To compare the distributions of the allele frequencies and folate cycle gene genotypes among the *MTHFR* 677 C>T (rs 1801133), *MTHFR* 1298 A>C (rs 1801131), *MTR* 2756 A>G (rs 1805087), and *MTRR* 66 A>G (rs 1801394) polymorphisms in patients with idiopathic scoliosis and in children without spinal deformity. To analyze the relationship between the studied molecular-genetic markers and development of scoliosis.
Materials and methods. Clinical and genetic examinations were performed in 48 children with idiopathic scoliosis and 32 healthy children. Molecular-genetic testing was performed by polymerase chain reaction.
Results and discussion. We found that the percentage of carriers of pathological alleles and genotypes was higher in children with idiopathic scoliosis than in the general population.
The number of pathological alleles and genotypes associated with the *MTHFR* (A1289C) and *MTRR* genes was significantly higher in patients with idiopathic scoliosis than in the control group.
Conclusion. We found that the percentage of carriers of pathological alleles and genotypes was higher in children with idiopathic scoliosis than in the population.

Keywords: idiopathic scoliosis; children; polymorphism; folate cycle genes.

ОЦЕНКА ТЕЧЕНИЯ ДЕФОРМАЦИИ ПОЗВОНОЧНИКА У ДЕТЕЙ С ИДИОПАТИЧЕСКИМ СКОЛИОЗОМ НА ОСНОВЕ ИССЛЕДОВАНИЯ ПОЛИМОРФИЗМА ГЕНОВ ФОЛАТНОГО ЦИКЛА

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Актуальность. Одной из распространенных ортопедических патологий у детей 10–18 лет является идиопатический сколиоз, который диагностируют в 2–3 % случаев в общей структуре популяции.
Цель работы — провести сравнительный анализ распределения частоты аллелей и генотипов генов фолатного цикла по полиморфизмам *MTHFR* 677 C>T (rs 1801133), *MTHFR* 1298 A>C (rs 1801131), *MTR* 2756 A>G (rs 1805087), *MTRR* 66 A>G (rs 1801394) у пациентов с идиопатическим сколиозом и у детей, не имеющих деформации позвоночника; проанализировать взаимосвязь исследованных молекулярно-генетических маркеров с развитием сколиоза.
Материалы и методы. Клинико-генетическое обследование было проведено у 48 детей с идиопатическим сколиозом и у 32 здоровых детей. Молекулярно-генетическое тестирование осуществляли методом ПЦР.

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Результаты исследования и обсуждение. Нами выявлено, что в группе детей с идиопатическим сколиозом процент носителей патологических аллелей и генотипов выше, чем в популяции. Установлено, что у пациентов с идиопатическим сколиозом по сравнению с контрольной группой исследования достоверно выше количество патологических аллелей и генотипов по генам *MTHFR* (A1289C) и *MTRR*.
Заключение. В результате исследования установлено, что в группе детей с идиопатическим сколиозом процент носителей патологических аллелей и генотипов выше, чем в популяции.

Ключевые слова: идиопатический сколиоз; дети; полиморфизм; гены фолатного цикла.

Introduction

Deformity of the spine is one of the most common orthopedic pathologies of childhood. In children 10–18 years old, idiopathic scoliosis is diagnosed in 2%–3% of cases in the overall population. However, the course of spinal deformity in patients with idiopathic scoliosis is different: in some, the curvature has a rapid rate of progression, whereas in others, the magnitude of the deformity remains practically unchanged until the end of growth [1].

Several groups of primary factors that affect the pathological process course in idiopathic scoliosis have been identified in the literature; namely, anatomical and anthropometric parameters of the spinal deformity, such as the magnitude of the apical vertebra, Cobb primary curve deformity angle, and specific rotation [2]; genetically inherited prerequisites, various mutations of genes [3–5]; characteristics of the surrounding tissue condition [6]; state of the endocrine system and hormonal disorders [7]; and concomitant anomalies in the development of the spinal canal and spinal cord [8, 9].

Presently, genetic analysis is one of the primary directions in the study of the etiology and pathogenesis of idiopathic scoliosis. Much research has been conducted on the relationship between the formation of spinal deformities and genetic polymorphisms and mutations. The genes encoding the connective tissue structure, such as fibrillin (*FBN1*), elastin (*ELN*), type 1 collagen A1 and A2 (*COL1A1, COL1A2*), type 2 collagen (*COL2A1*), and aggrecan (*ACAN*), have been studied. The results of those studies did not show the existence of a relationship between the polymorphism of these genes and the rate of progression of idiopathic scoliosis [10, 11].

Despite the fact that the genes of folate cycle enzymes have not been studied in patients with idiopathic scoliosis, these genes are responsible for the activity of enzymes of methylation reactions, which are responsible for many enzyme transformations, including melatonin metabolism. Given the fact that deficiency and anomalies in the melatonin signal system are one of the etiological factors of idiopathic scoliosis [12, 13], changes in genes responsible for coding in the activity of folate cycle enzymes, for example *MTHFR*, may be related to idiopathic scoliosis [14]. The genes *MTHFR, MTR,* and *MTRR,* are the most studied among the genes of the folate cycle. The quantity and quality of the end products of metabolism (folates) depend on the activity of the enzymes encoded by these genes [15, 16].

From the point of view of determining the treatment strategy of a patient with idiopathic scoliosis, it is very important to assess the nature of the spinal deformity at the early stages of deformity development and to identify a group of patients with a progressive course pattern [17]. This is necessary for the implementation of relevant therapy to correct curvature and prevent further development of curvature. Identification of genetic factors of the etiology of idiopathic scoliosis enables better understanding of the pathogenesis of the disease, prediction of the course of its development, and to prevent the need for possible surgical intervention.

The study **aim** was to analyze the polymorphism of folate cycle genes by polymerase chain reaction (PCR) in pediatric patients with the progressive type of idiopathic scoliosis.

Materials and methods

The study subjects were pediatric patients with idiopathic scoliosis of the third and fourth degrees with a progressive course. All patients and/or their representatives gave written informed consent for the processing of personal data and participation in the study. From 2016 to 2017, clinical and molecular genetic examinations were performed in 48 pediatric

Table 1

Distribution of patients according to spinal deformity variants

Variant of spinal deformity	Girls	Boys
Thoracic	27	5
Thoracolumbar	3	0
Lumbar	1	4
S-shaped	7	1
Total	38	10

patients with progressive idiopathic scoliosis aged 14–18 years with complete bone growth (4–5 points by Risser test). The examined patients included 10 boys and 38 girls. The deformity angle varied from 38° to 146° (average, 92°). The study group did not include children <14 and >18 years old as well as those with developmental defects of the spinal cord and spinal canal. Clinically, no neurological disorders were observed in any child. The study included patients with thoracic (32 patients), lumbar (5), thoracolumbar (3), and combined (8) idiopathic scoliosis grouped according to localization of the main scoliotic curves (Table 1).

Molecular genetic research was conducted in pediatric patients with idiopathic scoliosis. Polymorphic variants of the genes that produce key folate metabolite enzymes were studied, namely, *MTHFR* 677 C>T (rs 1801133), *MTHFR* 1298 A>c (rs 1801131), *MTR* 2756 A>G (rs 1805087), and *MTRR* 66 A>G (rs 1801394). The materials for molecular genetic testing were DNA samples of pediatric patients with a progressive course of idiopathic scoliosis isolated from peripheral blood leukocytes.

To compare the frequency distribution of alleles and genotypes of the polymorphisms under study, a control group was formed, which consisted of 32 children aged 14 to 18 years, without orthopedic pathology or spinal deformity. The enrollment criteria for the control group were healthy children aged 14 to 18 years with complete bone growth (4–5 points by Risser test).

Four polymorphisms (SNP) {3.1 [EN] Please expand the abbreviation} markers of three genes were genotyped: *MTHFR* 677 C>T (rs 1801133), *MTHFR* 1298 A>c (rs 1801131), *MTR* 2756 A>G (rs 1805087), and *MTRR* 66 A>G (rs 1801394).

Analysis of genetic polymorphisms was performed by using sets of SNP-Screen (Sintol, Russia) reagents to determine single-nucleotide DNA polymorphisms by performing real-time PCR on a cFX96 Touch™ Real-Time PCR Detection System analyzer (Bio-Rad, USA).

During the research, statistical processing was performed in the Statistics 6.0 software environment. The reliability of the differences between the observation groups was assessed by non-parametric paired Student's t-test with a two-sided distribution and by determination of the statistical reliability index. Differences were considered significant for $p < 0.05$.

Results and discussion

The genotype distribution results in the pediatric patients with idiopathic scoliosis group and control group are presented in Table 2.

It is known that the C677T genotype of the *MTHFR* gene is found at a rather high frequency (≤20%) in Caucasian populations in the Caucasian {1.5 [EN] Verify technical word choice} race. Simultaneously, the C677T genotype is found in 5%–15% of Europeans [18, 19]. The most studied mutation of the *MTHFR* gene is the variant with the cytosine (C) nucleotide in position 677 belonging to the exon 4 replaced by thymidine (T), which results in replacement of the amino acid residue of alanine with the valine residue at the folate binding site. Such polymorphism of *MTHFR* is referred to as C677T polymorphism and is inherited autosomally and recessively. In individuals homozygous for this mutation (T677T), the thermolability of *MTHFR* and the decrease in enzyme activity approximately ≤35% of the mean value are noted. The data obtained in the course of our work differ to some extent from the population values in Caucasians. In the control group of the study, based on literature data, a heterozygous genotype (C677T) was noted in 31% of the cases and in 40% of pediatric patients with idiopathic scoliosis, which exceeded these

Table 2

Distribution of genotypes in pediatric patients in the idiopathic scoliosis group and control group

Gene	Genotype	Idiopathic scoliosis group, % $n = 48$	Control group, % $n = 32$
MTHFR	C677C C677T T677T	54 40 6	56 31 13
MTHFR	A1298A A1298C C1298C	35* 50* 15	59* 28* 13
MTR	A2756A A2756G G2756G	58 40 2	62.5 37.5 0
MTRR	A66A A66G G66G	38* 19* 44	19* 47* 34

Note: * $p < 0.005$.

values in the European population. It also should be noted that the homozygous genotype (T677T) in the control group was found in 13% of cases, which was higher than in the group of pediatric patients with idiopathic scoliosis (6%) but corresponded to the average statistical population values of the Caucasian race in both groups.

Another variant of *MTHFR* gene polymorphism is the replacement of the nucleotide adenine (A) with cytosine (C) at position 1298. This polymorphism leads to the replacement of the glutamine residue with the alanine residue in the regulatory domain of the enzyme, which is accompanied by a small decrease in activity. In individuals homozygous for A1298C polymorphism, *MTHFR* activity is decreased to approximately 60% of normal [19, 20]. Polymorphism of the gene methylenetetrahydrofolate reductase (A1298C) has been less studied; the frequencies of genotypes A1298C and C1298C in the population are 20%–30%, respectively. In the Russian and foreign literature, there is no information on the isolated occurrence of homozygous and heterozygous polymorphisms of genes in the study groups. The frequency of the heterozygous genotype A1298C in Caucasians is 47.2% and that of homozygous C1298C is 8.8%. In the group of healthy children, the genotype A1298C was detected in 28% of the cases, which is significantly lower than the statistical data for Caucasians, and C1298C was detected in 13% of the cases, which is slightly higher. It should be noted that the genotypes A1298C and S1298S occurred significantly more frequently in our group of pediatric patients with idiopathic scoliosis than in the European population (based on published data); specifically, the heterozygous genotype was found in 50% of the cases, the homozygous genotype was found in 15% of the cases ($p < 0.005$), and two times more often in total (65%) than in the population as a whole (20%–30%).

The frequency of B_{12}-dependent methionine synthase (*MTR*: 2756 A>G) in the population of genotypes A2756G and G2756G has previously been found to be 20%–30% [19, 21, 22]. The frequencies of genotypes A2756G and G2756G were significantly higher in both the healthy children group and pediatric patients with idiopathic scoliosis group than in the general population (42% and 37.5%, respectively), but the differences were not significant. Therefore, evaluation of this polymorphism cannot be used as a clinical diagnostic criterion of the course of spinal deformity.

Polymorphism of the gene methionine synthase reductase (*MTRR*) (A66G) causes a disorder in homocysteine metabolism and an increase in its concentration in the blood. *MTRR* is associated with neural tube developmental defects. In the population, the frequency of genotypes A66G and G66G is 40%–50% [19]. In the present study, the frequencies of genotypes A66G and G66G were higher in both groups of patients than in the population; 57% in the study group and 66% in the control group, but the difference was not significant. In the healthy children group, the heterozygous genotype (A66G) was more common (47% of cases) and the genotype G66G was noted in 19% of cases;

in the pediatric patients with idiopathic scoliosis group, the A66G genotype was found in 19% of the cases and genotype G66G was found in 38% of the cases ($p < 0.005$). The differences in genotypes for A66G polymorphism between the patients with idiopathic scoliosis and the healthy children group suggest a higher frequency of homozygous G66G polymorphism in pediatric patients with spinal deformity and may be one of the criteria characterizing the progressive nature of vertebral column curvature in pediatric patients.

Conclusion

We found that in the group of pediatric patients with idiopathic scoliosis, the percentages of carriers of pathological alleles and of genotypes were higher than the average values in the population. Pathological alleles and genotypes for the genes *MTHFR* (A1289C) and *MTRR* were significantly higher in pediatric patients with progressive idiopathic scoliosis than in the controls ($p < 0.005$). A higher frequency of the gene polymorphism *MTRR* was noted in pediatric patients than in the population, and there were significant differences in the frequencies of genotypes AG and GG between the progressive idiopathic scoliosis pediatric patients than in the controls. The results obtained can be the basis for assessing the course of spinal deformity in pediatric patients with idiopathic scoliosis and the rate of progression of vertebral column curvature in patients with this pathology, which in turn enables selection of patients for the risk group with a progressive course of deformity and to promptly determine the best complex therapy for this group of children.

Funding and conflict of interest

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