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Quantitative Assessment of Severity in Gastroduodenal Pathology in Children

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Abstract: Relevance. The immune response to H. pylori infection in children is an earlier pathological response and can serve as a kind of model for studying the characteristic course of H. pylori. In the conditions of the Republic of Uzbekistan, such studies have not been carried out, at the same time, the tendency towards weight gain, rejuvenation and a high frequency of complications dictate the need to study this issue. Purpose of the study. To study the clinical and prognostic significance of the rs1800629 (G308A) polymorphism of the TNF gene in children with gastroduodenal pathology, depending on H. pylori infection. Patients and methods. Examined 182 children aged 7 to 18 years with gastroduodenal pathology. Of these, 98 (53.8%) patients with HP associated pathology and 84 (46.2%) patients with HP negative pathology of the gastroduodenal zone. The rs1800629 (G-308A) polymorphism of the TNF gene was determined. Statistical data processing has been carried out. Results. The presence of the GA TNF-a genotype rs1800629 is an unfavorable prognostic marker in the development of this pathology in the presence of HP infection. At the same time, the GG genotype rs1800629 is a protective genotype for the underlying pathology, regardless of the presence of HP infection. Conclusion. The presence of the GA genotype TNF-a rs1800629 is an unfavorable prognostic marker in the development of this pathology in the presence of HP infection. GG genotype rs1800629 is a protective genotype for the underlying pathology, regardless of the presence of HP infection.

Keywords: children, gastroduodenitis, peptic ulcer, Helicobacter pylori, immunology, genetics.

Relevance Helicobacter pylori (H. pylori) infection is currently considered as the leading etiopathogenetic factor of peptic ulcer (PU) and chronic gastritis (CG) in childhood [1]. The results of large-scale studies have shown that peptic ulcer disease associated with Helicobacter pylori infection accounts for 70-80% of cases of duodenal ulcer and 50-60% of gastric ulcers [2]. There is increasing evidence of the role played by Helicobacter pylori infection in the occurrence and development of gastric cancer [3]. Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine synthesized predominantly by macrophages and monocytes. that plays an important role in initiating and enhancing the immune-inflammatory response to H. pylori infection [4]. At the cellular level, TNFα stimulates the production of pro-inflammatory cytokines such as interleukin-1, -6, -8. Responsible for immune and inflammatory response, including necrosis [5, 6]. The genes encoding them are one of the main candidate genes for YB. Polymorphic variants of cytokine genes and their receptors can have a significant impact on the risk of developing gastric and duodenal ulcers. In addition, the bacterium, inducing an immunoinflammatory reaction, contributes to the death of the macroorganism's own cells, which causes the development of deep dystrophic and atrophic changes in the gastric mucosa with the phenomena of metaplasia and dysplasia. Further hyperplastic

processes lead to the development of gastric cancer [7]. In this regard, early detection, timely diagnosis and treatment of children with precancerous conditions and changes in the gastric mucosa are relevant. Nowadays, there are studies conducted to study the immune response against H. pylori infection, which are reflected in foreign literature. Single nucleotide polymorphisms in some genes encoding cytokines alter the expression of cytokines in the coolant and may affect the clinical outcome of H. pylori infection [8]. Polymorphisms that lead to increased levels of IL-1β and TNFα, as well as polymorphisms that cause a decrease in IL-1RA expression, cause more severe inflammation and are associated with an increased risk of developing atrophic gastritis and gastric cancer [9]. Data on the features of the production of proinflammatory cytokines in the coolant in children in the literature are scarce. According to some data, in children, as in adults, there is a predominance of the immune response to H. pylori with the participation of Th1 with the production of the corresponding cytokines [10]. According to other data, the cytokine response in the coolant to H. pylori in children may be lower than in adults. This may protect children from developing severe gastrointestinal diseases such as stomach ulcers. Several studies have shown increased local production of IL-1β, TNF-α, IL-8, IL-18, and IFN-γ in H. pylori-infected children compared to uninfected children. At the same time, there was no increase in the production of IL-4[11]. H. pylori infection affects the entire coolant due to the presence of various pathogenic factors in this microorganism. H. pylori infection is chronic in which IFN-γ, IL-12, IL-18, IL-23, TNF-α are produced. The development of inflammatory and immune responses leads to an increase in the production of pro-inflammatory cytokines, such as IL-1β, IL-8, TNF-α, IFN-γ, the local production of cytokines in the coolant of which can serve as a marker of H. pylori infection, microbial colonization density and severity diseases. The immune response to H. pylori infection in children is an earlier pathological response and can serve as a model for studying the characteristic course of H. pylori. In the Republic of Uzbekistan, such studies have not been conducted, at the same time, the tendency to gain weight, rejuvenation and a high incidence of complications dictate the need to study this issue. Purpose of the study. Study of the clinical and prognostic significance of the rs1800629 (G308A) polymorphism of the TNF gene in children with gastroduodenal pathology depending on H. Pylori infection. Materials and methods 182 children aged 7 to 18 years with gastroduodenal pathology were examined. Out of them, 98 (53.8%) patients with HP associated pathology and 84 (46.2%) patients with HP negative pathology of the gastroduodenal zone. The age of the patients ranged from 7 to 18 years, including 79 (43.4%) boys and 103 (56.6%) girls. 28 (15.4%) of them had peptic ulcer, 154 (84.6%) had chronic gastroduodenitis. The polymorphism rs1800629 (G-308A) of the TNF gene was determined. DNA isolation The material for DNA extraction was venous blood from the cubital vein with a volume of 3-5 ml (Beckton-Dickinson vacutains were used for blood sampling) with an anticoagulant/preservative 15% tripotassai EDTA (ethylenediantetraacetic acid). To obtain genomic DNA, a two-stage method of lysis of blood cells was used. Methods for detecting allelic variations in genes. Polymerase chain reaction (PCR) was performed on a Rotor-Gene-2000 heat cycle (Corbett Research) using appropriate primers and 10 µl of a PCR mixture (manufactured by «NPO Lyteh») containing 2 mM MgCl2, Taq DNA polymerase, and «Cresol red». Statistical processing of the results was carried out using statistical software packages and a number of formulas. In medical statistics, the following indicators are generally accepted: 1. The calculation of the frequency of genes in healthy and sick people is carried out according to the formula of the ratio of the number of a certain allele to doubling the total number of individuals in the sample. 2. The main indicator for haplotypes is bonds disequilibrium (LD). 3. The frequency of genes is determined taking into account the Hardy-Weinberg law for the biallelic system. A $\chi 2$ value greater than 3.841 (corresponding to $p < 0.05$) is considered significant. Results and discussion The TNFA gene is located on the short arm of the 6th chromosome in the p21.3 region and contains 4 exons. There are data on the relationship between the TNFA gene polymorphism and its content. Several SNPs of the TNFA gene have been identified: -1031T/C, - 863C/A and -857C/A, -308G/A and -238G/A. Among them, the most studied are two polymorphic variants of the TNFA gene: - 238G/A -308G/A, which affect the production of this cytokine in different directions: in position 308, the substitution of guanine for adenine increases the production of the cytokine TNFA. Comparison of the frequency of alleles and genotypes of polymorphic markers of the TNFα - 308G/A gene showed that in patients with HP the allele frequency was 4 times higher than in controls (35.16 and 8.42%, respectively; OR

= 4.64; 95% CI: 2.573> 4.64> 8.368; χ2=29.255). At the same time, the G allele of the studied polymorphism was much less common, whose in the control (82.42 and 91.58%; OR = 0.216; 95% CI: 0.119> 0.216> 0.389; χ2=29.255) (Table 1). Table 1 Distribution of alleles and genotypes of TNF-a rs1800629 in the group of CGD patients with H. pillory Genotyp Number of persons Control n=91 % n=95 % χ2 OR (95% CI) G 150 82,42 174 91,58 29,255 0.119 >0.216> 0.389 A 64 35,16 16 8,42 2.573 >4.64> 8.368 GG 59 64,84 79 83,16 8,15 0.188 >0.373> 0.743 GA 32 35,16 16 16,84 8,15 1.345 >2.678> 5.33 AA 0 0,00 0 0,00 0.119 >0.216> 0.389 Note. χ2 – Pearson's reliability indicator; OR - relative risk; Comparison of indicators of TNFα -308G/A genotypes by GG genotype showed that in patients with HP these indicators were 1.3 times higher than those in control groups OR = 0.373; 95% CI: 0.188 > 0.373 > 0.743; χ2=8.15. The frequency of occurrence of the heterozygous GA genotype in patients with HP was almost 2 times higher than the control indicator OR = 2.678; 95% CI: 1.345 > 2.678 > 5.33; χ2=8.15. As already described above, a significant difference was found in the frequency of occurrence of the A allele, the TNFα -308G/A polymorphism under study, but no homozygous AA genotype was detected during genotypic analysis. A comparative study of the distribution of frequencies of alleles and genotypes of polymorphic markers of the TNFα -308G/A gene in patients without HP and in control group showed a statistically significant increase of 1.25 times in the frequency of the A allele in patients from control group; OR=2.599; 95% CI: 1.395 > 2.599 > 4.843; χ2=9.515 (Table 2). The G allele was found much less frequently than in the control group; OR=0.385; 95% CI: 0.206 > 0.385 > 0.717; χ2=9.515. The study of TNFα -308G/A genotypes for the GG genotype did not show significant differences between both groups; OR=0.746; 95% CI: 0.356 > 0.746 > 1.562; χ2=0.6). The indicator of the heterozygous genotype GA was 1.3 times higher than the one in patients without HP and in the control group; OR=1.34; 95% CI: 0.64 > 1.34 > 2.80; χ2=0.6). As already described above, a significant difference was found in the frequency of occurrence of the A allele of the studied TNFα -308G/A polymorphism, but no homozygous AA genotype was detected during genotypic analysis. ЕВРАЗИЙСКИЙ ВЕСТНИК ПЕДИАТРИИ 2(13) 2022 ISSN 2181-1954. EISSN 2181-1962 83 Table 2 Distribution of alleles and genotypes of TNF-a rs1800629 in CGD patients without H. pilory Genotype Number of persons Control χ2 OR (95% CI) n=89 % n=95 % G 159 89,33 174 91,58 9.515 0.206 >0.385> 0.717 A 38 21,35 16 8,42 1.395 >2.599> 4.843 GG 70 78,65 79 83,16 0.606 0.356 >0.746> 1.562 GA 19 21,35 16 16,84 0.606 0.64 >1.34> 2.80 AA 0 0,00 0 0,00 Note. χ2 – Pearson's reliability indicator; OR - relative risk. Next, we compared these scores between of the groups. We found that the frequency of alleles and genotypes of polymorphic markers of the TNFα -308G/A gene in patients with HP was 1.6 times higher than in patients without infection; OR=1.785; 95% CI: 1.128 >1.785 > 2.826; χ2=6.197 (Table 3). Table 3 Distribution of alleles and genotypes of TNF-a rs1800629 in the group of CGD patients with H.pilory and without infection Genotip HP (+) Control n=89 % n=95 % χ2 OR (95% CI) G 150 82,42 159 89,33 6.197 0.354 >0.56> 0.887 A 64 35,16 38 21,35 1.128 >1.785> 2.826 GG 59 64,84 70 78,65 4,23 0.257 >0.5> 0.973 GA 32 35,16 19 21,35 4,23 1.028 >1.998> 3.885 AA 0 0,00 0 0,00 The G allele of the studied polymorphism was less common in the group with HP infection; OR=0.56; 95% CI: 0.354 > 0.56 > 0.887; χ2=6.197. Analysis of the GG genotype established a small but significant difference between patients of both groups; OR=0.5; 95% CI: 0.257 > 0.5 > 0.973; χ2=4.23). The heterozygous GA genotype was also detected more often in patients with HP; OR=1.99; 95% CI: 1.028 > 1.998 > 3.885; χ2=4.23). No homozygous AA genotype was found. Conclusion The presence of the GA genotype TNF-a rs1800629 is an unfavorable prognostic marker in the development of this pathology in the presence of HP infection. GG genotype rs1800629 is a protective genotype for the underlying pathology, regardless of the presence of HP infection.

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