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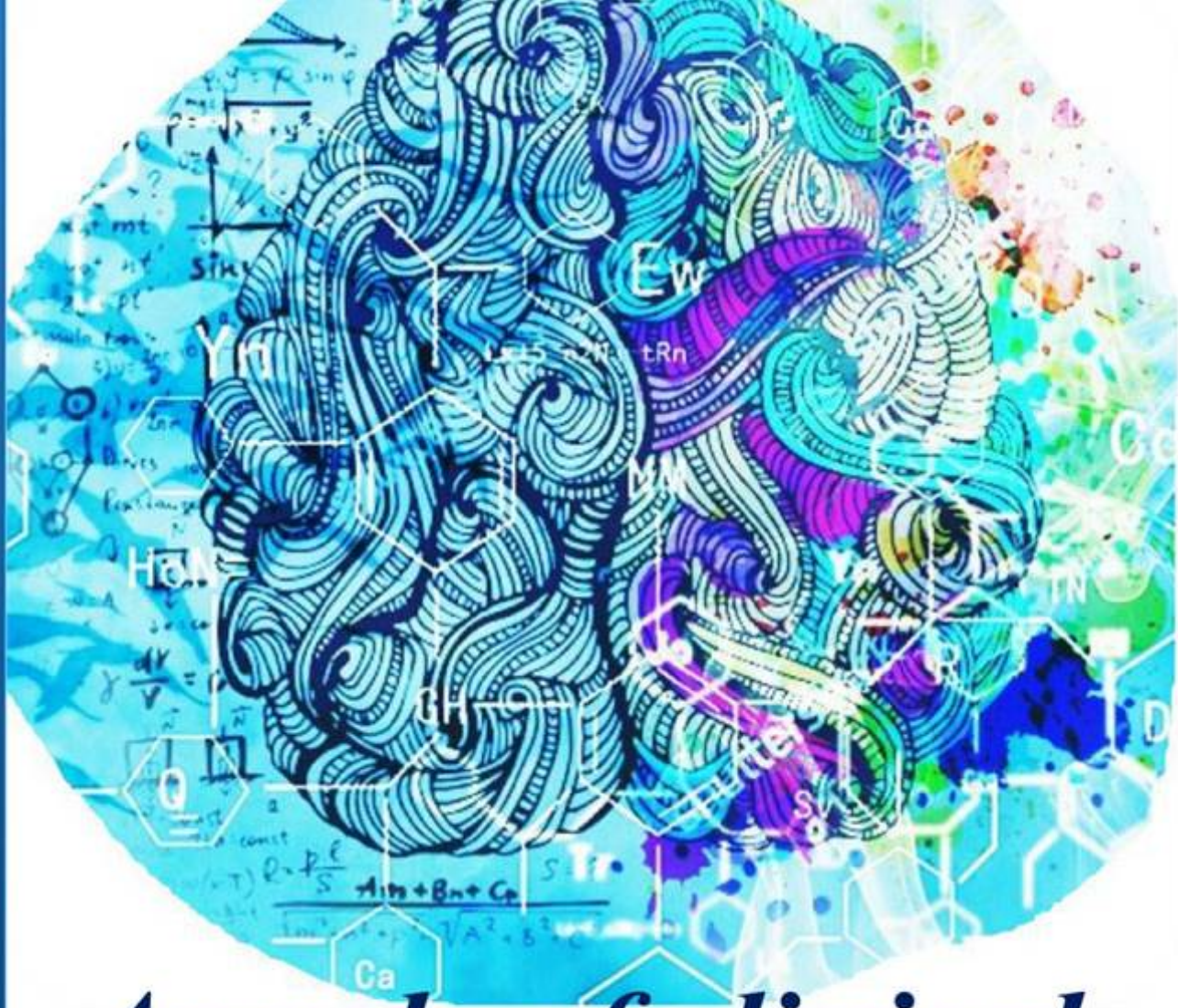

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DEVELOPMENT OF GASTROPATHY AGAINST THE BACKGROUND OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN PATIENTS WITH RHEUMATOID ARTHRITIS AGAINST THE BACKGROUND OF VIRULENT GENES OF HELICOBACTER PYLORI

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ABSTRACT

The article provides data on the result of a molecular genetic study of the genotypic characteristics of Helicobacter pylori in the formation of NSAIDs of gastropathy in patients with rheumatoid arthritis. Purpose of the study. Molecular-genetic study of the genotypic features of H. pylori in the formation of NSAID gastropathy in RA patients for the prevention of gastroduodenal lesions. Materials and research methods. The research is based on the genomic DNA of H. pylori, isolated from a biopsy of the antrum of 82 patients with RA and 22 healthy individuals. The genotype of H. pylori CagA, vacam1, vacam2, vacAs1, vacas2, vacas1b, vacas1c, icea1, icea2, HP was determined in biopsy samples. Results. Thus, according to the molecular genetic study, the pathogenic strain VacA m2 (x^2=4,12 p=0.011), IceA 2 (=6,71 p=0.036) prevails in patients with RA of the 2nd degree of activity. Conclusion. Our preliminary results suggest that the H. Pylori vaca m2 and icea 2 may be considered as additional markers of NSAID-gastropathy in rheumatoid arthritis.

Keywords: H. Pylori, rheumatoid arthritis, gastropathies, pcr, molecular genetic study.

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РАЗВИТИЕ ГАСТРОПАТИИ НА ФОНЕ НЕСТЕРОИДНЫХ ПРОТИВОВОСПАЛИТЕЛЬНЫХ СРЕДСТВ У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ НА ФОНЕ ВИРУЛЕНТНЫХ ГЕНОВ HELICOBACTER PYLORI

АННОТАЦИЯ

В статье приводятся данные о результате молекулярно-генетического исследования генотипических особенностей Helicobacter pylori в формировании НПВС гастропатии у больных с ревматоидным артритом. Цель исследования. Молекулярно-генетическое исследование генотипических особенностей Helicobacter pylori в формировании НПВС гастропатии у больных РА с целью профилактики гастродуоденальных поражений. Материалы и методы исследования. Материалом исследования послужила геномная ДНК H. pylori., выделенная из биоптата антрального отдела желудка 82 больных РА и 22 здоровых

лиц. В биопсийных образцах определяли генотип H.pylori cagA, vacAm1, vacAm2, vacAs1, vacAs2, vacAs1b, vacAs1c, iceA1, iceA2, HP. Результаты. По данным молекулярно-генетического исследования у больных с РА 2 степени активности превалирует патогенный штамм VacA m2 (x^2=4,12 p=0.011), IceA 2 (=6,71 p=0.036). Заключение. Полученные предварительные результаты позволяют предположить, что гены H. Pylori VacA m2 и IceA 2 могут рассматриваться как дополнительные маркеры возникновения НПВС-гастропатии при ревматоидном артрите.

Ключевые слова: H. pylori, ревматоидный артрит, гастропатия, пцр, молекулярно-генетическое исследование.

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РЕВМАТОИД АРТРИТ БИЛАН ОҒРИГАН БЕМОРЛАРДА HELICOBACTER PYLORI ВИРУЛЕНТ ГЕНЛАРИ ФОНИДА НОСТЕРОИД ЯЛЛИҒЛАНИШГА ҚАРШИ ДОРИЛАР ТАЪСИРИДА ГАСТРОПАТИЯНИНГ РИВОЖЛАНИШИ

АННОТАЦИЯ

Мақолада ревматоид артрит билан оғриган беморларда ностероид яллиғланишга қарши дори воситалари (НЯҚДВ) гастропатияси шаклланишида Helicobacter pylori генотипик хусусиятларининг молекуляр-генетик тадқиқот натижалари келтирилган. Тадқиқот мақсади: РА билан оғриган беморларда гастродуоденал шикастланишларнинг олдини олиш учун НЯҚДВ гастропатияси шаклланишида Helicobacter pylori генотипик хусусиятларини молекуляр-генетик ўрганиш. Тадқиқот материаллари ва усуллари: Тадқиқот материали сифатида 82 нафар РА билан касалланган бемор ва 22 нафар соғлом шахснинг ошқозон антрал қисмидан олинган биоптатдан ажратиб олинган H. pylori геномик ДНКси хизмат қилди. Биопсия намуналарида H.pylori cagA, vacAm1, vacAm2, vacAs1, vacAs2, vacAs1b, vacAs1c, iceA1, iceA2, HP генотиплари аниқланди. Натижалар: Молекуляр-генетик тадқиқот маълумотларига кўра, 2-даражали фаолликка эга РА билан оғриган беморларда VacA м2 (x2=4,12 п=0,011) ва IceA 2 (x2=6,71 п=0,036) патоген штаммлари устунлик қилади. Хулоса: Олинган дастлабки натижалар шуни кўрсатадики, H. pylori VacA м2 ва IceA 2 генлари ревматоид артритда НЯҚДВ гастропатияси пайдо бўлишининг қўшимча маркерлари сифатида қаралиши мумкин. Натижалар. Молекуляр-генетик тадқиқот маълумотларига кўра, фаоллик даражаси 2 бўлган РА билан оғриган беморларда ВасА м2 (x2=4,12 p=0,011), ИсеА 2 (=6,71 p=0,036) патоген штамми устунлик қилади. Хулоса. Олинган дастлабки натижалар H. pylori бактериясининг VacA м2 ва IceA 2 генларини ревматоид артритда ностероид яллиғланишга қарши воситалар (НЯҚДВ) гастропатияси ривожланишининг қўшимча белгиловчилари сифатида кўриб чиқиш мумкинлигини тахмин қилишга имкон беради.

Калит сўзлар: H. pylori, ревматоид артрит, гастропатия, ПЗР, молекуляр-генетик текширув.

Introduction. Rheumatoid arthritis (RA) is a progressive autoimmune disease of unknown etiology with predominant joint damage, characterized by the development of chronic erosive arthritis and frequent systemic inflammation of internal organs [1]. NSAIDs are an important component of the complex therapy of rheumatic diseases. At least 68.5% of patients with rheumatoid arthritis are constantly taking NSAIDs [2]. Therefore, among patients with RA, the highest incidence of NSAID-associated gastropathy, erosive and ulcerative lesions complicated by gastrointestinal bleeding and other complications [3]. Therefore, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is also a factor in ulcerogenesis. However, the influence of pathogenic factors of H. pylori on the likelihood of erosive and ulcerative damage to the gastroduodenal zone induced by NSAID intake has not been sufficiently studied.

Numerous studies have focused on the prevalence and role of putative H. pylori virulence genes in the pathogenesis of diseases. The genomic sequence of H. pylori is very diverse and is a powerful tool for understanding evolution and disease, for identifying factors that cause a higher risk of severe consequences, and for finding new approaches to therapy [4, 11]. Assessment of the pathogenicity of Helicobacter pylori is relatively difficult, as H. pylori isolates exhibit a high degree of geographic variation, with certain H. pylori genotypes associated with a more severe clinical outcome in some regions, while in other studied populations they are presented as practically harmless options [7, 12]. Moreover, differences between East Asian and Western strains support the hypothesis that the degree of gastroduodenal pathology depends on the complex relationships between host genetics, environmental factors, and combinations of different H. pylori virulence genes [8]. Although the importance of most H. pylori virulence genes has not et been uniformly explained, knowledge of their role in pathogenesis as well as disease outcome has improved significantly over the past two decades. A number of studies have analyzed the relationship of Helicobacter pylori genes (cagA, vacAm1, vacAm2, vacAs1, vacAs1a, vacAs1b, vacAs1c, vacAs2, babA, iceA1, iceA2, dupA) with the development of gastritis, gastroduodenal ulcers, and stomach cancer [9].

Purpose of the study. Molecular genetic study of the genotypic features of Helicobacter pylori in the formation of NSAID gastropathy in patients with RA in order to prevent gastroduodenal lesions.

Material and methods. 82 patients with rheumatoid arthritis (71 (84%) women and 11 (16%) men) who were inpatient treatment in the rheumatology department of the Tashkent Medical Academy multidisciplinary clinic and who had been using NSAIDs for a long time were examined. The control group consisted of 22 healthy individuals. On the basis of laboratory examinations, the patients were divided into 2 groups, according to the degree of activity of R.A. The material for the study was the genomic DNA of H. pylori, isolated from a biopsy specimen of the antrum of the stomach. Molecular genetic studies were carried out at the Republican Scientific and Practical Medical Center of Hematology of the Republic of Uzbekistan. The molecular genetic part of the work included several stages: 1. Selection and optimization of the operation of oligoprimer systems for H. pylori virulence genes. 2. Collection of biological material 3. Extraction of DNA from biological material. 4. Carrying out PCR. 5. Conducting electrophoresis and visualizing the results. Mutations were identified by polymerase chain reaction (PCR) using known primer sequences kindly provided by the Center of High Technologies. PCR was performed using kits from Litekh (Russia) and Amplisens (Russia). In all examined individuals, the genotype of H. pylori cagA, vacAm1, vacAm2, vacAs1, vacAs2, vacAs1b, vacAs1c, iceA1, iceA2 was determined from biopsy samples. The estimation of the distributions deviation of the studied DNA genotypes polymorphisms from the canonical Hardy-Weinberg, distribution was carried out using the computer program for the analysis of genetic data “GenePop” (“Genetics of Population”) (http://wbiomed.curtin.edu.au/genepop). The software package "OpenEpi 2009, Version 2.9" was used as a calculation tool.

Results and discussion. The human bacterial pathogen Helicobacter pylori, the subject of intensive research since its first description in 1984, affects half of the world's population [6]. The first H. pylori genome sequence was published in 1997 (Tomb et al. 1997), and it was the first bacterium for which two genome sequences became available in 1999 (Alm et al. 1999). These two strains showed high levels of genomic differences, both at the sequence level and at the predicted gene level. Helicobacter pylori lends itself to natural transformation, and mutations, recombination and frequent genetic exchange have led to a high level of genome variability, which can be observed over time even in one patient (Kuipers et al. 2000).) The chromosome contains genes that encode a cluster of urease genes, different cytotoxins and cag island of pathogenicity. Toxins include cytotoxin, a stretching cytotoxin, vacuolizing cytotoxin (VacA), which induces apopoptosis of host epithelial cells (cell death), and a cytotoxin-associated antigen (CagA), which leads to altered host cell signaling pathways. The CagA protein is translocated into host cells by the type IV secretion system encoded by the cag pathogenicity islet [5].

Our studies made it possible to select and optimize the operation of H. pylori gene oligoprimer systems. The developed methodology became the basis for genotyping of H. pylori genes in RA patients with and without gastropathy, which made it possible to conduct preliminary molecular genetic studies to determine the frequency of occurrence of allelic variants of the above genes among conditionally healthy and sick patients. Optimization of molecular genetic methods for detecting H. pylori virulence genes will help increase the efficiency and reduce the cost of the study.

Many studies have assessed the influence of genes of the H. pylori microorganism on the development of gastritis, peptic ulcer and stomach cancer, however, the information available in the literature on the role of the H. pylori genotype in the development of gastroduodenal diseases is contradictory.

As a result of the molecular genetic study, no statistically significant differences were found between the groups of patients in the degree of activity ($p > 0.05$). But at the same time, in the group of patients with the 2nd degree of RA activity, the spectrum of H. pylori genotypes was significantly different, vacAm2 and iceA2 were much more common. The vacA gene has 2 regions: signal - s (signal) and middle - m (middle). In the signaling s-region of the gene, two allelic variants are distinguished - s1 and s2. The middle m-region also has two allelic types - m1 or m2. The amount of VacA cytotoxin generated depends on the genotype of the strain. H. pylori strains vacAs1m1 produce the greatest amount of VacA cytotoxin and are more often associated with peptic ulcers [5].

Genes cagA, vacAm1, vacAs1, vacAs1a, vacAs1b, vacAs1c, iceA1 were equally often detected in patients with 1 and 2 degrees of RA activity. In patients who constantly took NSAIDs before therapy with Diclofenac sodium and continued to take them in the future, did not lead to a change in the frequency of the spectrum of H. pylori genotypes. The results of molecular genetic studies are presented in table 1.

Table 1

Indicators of molecular genetic study of H. pylori virulence genes in patients with RA of I and II degrees of activity

H. pylori genotypes	RA of the 1st degree of activity N= 33		RA of the 1st degree of activity N=49		healthy individuals N=22		Statistics
	N	%	N	%	N	%	
cagA	16	48	21	43	7	31	x^2=0,05 p=0.11
vacAm1	17	50	22	45	5	22	x^2=0,20 p=0.712
vacAm2	14	43	34	70	-	-	x^2=4,12 p=0.011
vacAs1	13	40	17	35	4	18	x^2=0,09 p=0.671
vacAs2	8	25	29	60	-	-	x^2=0,55 p=0.550
vacAs1b	2	6	3	7	1	5	x^2=0,09 p=1.09
iceA1	7	22	11	23	3	14	x^2=0,90 p=1.09
iceA2	10	30	25	52	-	-	x^2=6,71 p=0.036

Thus, according to the data of a molecular genetic study, the pathogenic strain VacA m2, IceA 2 prevails in patients with RA of the 2nd degree of activity.

Conclusion. Our preliminary results suggest that H. Pylori genes VacA m2, IceA 2 can be considered as an additional markers of NSAID gastropathy in rheumatoid arthritis.

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