RESEARCH ARTICLE

MODERN ASPECTS TO THE PROBLEM OF THE PREVALENCE OF HELICOBACTER PYLORI ASSOCIATED STOMACH DISEASES IN UZBEKISTAN

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ABSTRACT

Introduction. We studied the regional epidemiological and genetic characteristics of the prevalence of *Helicobacter pylori* among the population of Uzbekistan. The work is based on the totality of the results of clinical, biochemical, immunological, genetic and instrumental research methods. **Materials and Methods.** It was established that Uzbekistan belongs to the regions with a high degree of *H. pylori* infection of the population (80%). 84% of the population of Uzbekistan have a mixed IceA1- / IceA2-genotype CagA. In peptic ulcer disease, the pathogenic strain CagA + VacA s1, VacA m2 and IceA 1,2 prevails, in chronic gastritis (type B) associated with *H. pylori*, the strain Cag + VacA s1, VacA m2 and IceA 1. **Results and Discussion.** The level of resistance of *H. pylori* strains to clarithromycin reaches 13.3%. Prolongation of eradication therapy up to 10 days and the addition of BTD to it makes it possible to increase the efficiency of *H. pylori* eradication up to 95%. **Conclusion.** Due to the presence of HP resistance to clarithromycin in 13.3% of cases and taking into account the low effectiveness of triadotherapy (72.5%), it is advisable to use quadritherapy with the inclusion of BTD in the standard of treatment, which contributes to an increase in the eradication efficiency up to 95%.

KEYWORDS

genetic research, *Helicobacter pylori*, gastric ulcer, chronic gastritis.

1. INTRODUCTION

Thanks to the rapid development of scientific technologies, the widespread introduction of innovative advances in science and technology into clinical practice, it became possible to study the human genome, to recognize the molecular-genetic basis of various pathological conditions. One of these pathological conditions is *Helicobacter pylori* (Hp) - associated human diseases. Undoubtedly, the discovery of Hp and the determination of its role in the origin of pathological conditions in the stomach and duodenum is one of the greatest achievements of medical science (Akifumi et al., 2008; Ford et al., 2004). According to NIH-consensus (1999) Hp-associated pathologies refer to "new" infections that target the organs of the upper level of the gastrointestinal tract (GIT) (Hooi et al., 2017).

According to various authors, helicobacteriosis is the most common infection in the world and has a correlation with age (Logan et al., 2017; Hooi et al., 2017; Maastricht, 2005). A group of researchers from the World Organization of Gastroenterologists (OMGE), in the course of many years of comprehensive study of the problem, came to the conclusion that HP-associated diseases have a global scale and are directly proportional to the level of development of countries (Malfertheiner et al., 2017; McNicholl et al., 2019; Savoldi et al., 2018). Thus, HP is widespread and infects half of the world's population - its prevalence is very high in developing countries and low in developed countries. In general, the global distribution of HP in the world exceeds 50%. Age, ethnicity, gender, geographic location and socioeconomic status are the main factors influencing the incidence and prevalence of HP infection. The main reasons for the variation in incidence are social and economic differences between populations.

It is known that HP is a recombinant, which occurs in it much more often

than in other species, as well as a high frequency of mutations of this microbe (Sugano et al., 2015; Vaira et al., 2007). A number of researchers argue that there is a high variability of HP, which distinguishes it from other microbes.

When studying *H. pylori* in residents of 20 countries of the world, certain differences in genotypes were established. However, in the regions of Central Asia, in particular in Uzbekistan, such studies have not been carried out. In addition, there is a tendency towards a steady decrease in the effectiveness of *H. pylori* eradication up to 70% against the background of standard first-line therapy, and in some countries - up to 60%. If in some countries of Western Europe the resistance to clarithromycin in untreated patients was only 0–2% and did not affect eradication rates, in many centers of Europe it reached 8–15% or more. In Asia and a number of European countries, this indicator was 60% (1.4). Studies of *H. pylori* resistance to clarithromycin in Uzbekistan have not been conducted, which complicated the choice of eradication regimens.

Based on the foregoing, the purpose of this study was to study the regional characteristics of the prevalence of *Helicobacter pylori* among the population of Uzbekistan by studying the epidemiological and genetic aspects.

2. MATERIALS AND METHODS

Studies of patients with HP included clinical, biochemical, immunological, genetic and instrumental research methods. *H. pylori* was verified using 2 methods: urease breath test and direct invasive method — determination of *H. pylori* in the gastric mucosa, using the CLO test.

To identify the genotypic characteristics of *H. pylori* contamination in the

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population of Uzbekistan, 100 biopsy samples were examined from patients who received inpatient treatment at the department of gastroenterology of the State Institution "RSNPMCTiMR". The genetic part of the research was carried out at the Institute of Biological Chemistry of the Academy of Sciences of the Republic of Uzbekistan. The material for the molecular genetic study of mutations was genomic DNA stored at -20 ° C. Mutations were determined by real-time polymerase chain reaction (RT-PCR) using primers and probes.

Genomic DNA was isolated from each biopsy sample using Diatom™ DNA Prep 200 reagent kits (manufactured by IsoGen Laboratory LLC). DNA extraction was carried out according to the standard DNA extraction protocol for the Diatom™ DNA Prep 200 reagent kit with a modification of the lysis step for up to 16 hours at 37 ° C. The DNA supernatant was directly genotyped by PCR amplification. PCR analysis was performed using the GenePak™ PCR Core kit for PCR amplification of DNA (manufactured by IsoGen Laboratory). PCR amplification was carried out according to a modified protocol.

All HP-positive patients were prescribed eradication therapy. 40 patients of the first group received standard triadotherapy - a proton pump inhibitor (PPI), amoxicillin and clarithromycin for 7 days, 60 patients of the second group - quadritherapy - PPI + amoxicillin + clarithromycin and bismuth tripotassium dicitrate (BTD) for 10 days. The effectiveness of therapy was assessed after 28-30 days by the C13-urease breath test.

3. RESULTS AND DISCUSSION

The analysis of the obtained results showed that the prevalence of HP in Uzbekistan, on average, exceeds 80% in the population (Fig. 1).

Consequently, Uzbekistan belongs to the regions with a high degree of HP infection. Moreover, 1367 identical genes with the European strain HP26695 and 1162 genes identical to the genes of the African strain J99 were found. These genes make up the functional core of the HP genome.

Figure 1: Frequency of detection of HP contamination in the context of regions

Two gene clusters were identified - zones of plasticity, where the proportion of strain-specific genes is 79% for the zone of plasticity HP0423 - HP0466 and 37% for the zone of plasticity HP0982 - HP1028. Among the individual groups, the genes responsible for DNA metabolism and the proteins of the cell wall differed to a greater extent in strain heterogeneity. Evaluation of the epidemiological distribution of HP genotypes showed that the CagA + variant prevails in all regions of the republic (Fig. 2). VacA s1m1 was more often recorded in the Aral zone (RKK and Khorezm region), VacA s1m2 - more often in eastern Uzbekistan (Tashkent and Namangan regions). A large amount (84%) of the mixed IceA1 / IceA2 genotype was found in Khorezm. In other regions, the IceA1 allele of this gene is dominant.

Figure 2: Virulence Hp (CagA + and CagA-)

The study also identified the genotypes of the bacteria associated with

various diseases of the stomach. In patients with chronic gastritis, the prevailing strain is Cag + VacA s1, VacA m2 and IceA 1, in patients with gastric ulcer - strain CagA + VacA s1, VacA m2, IceA 1.2. In turn, the results obtained contribute to the adaptation of the current clinical protocols and standards for the treatment of HP associated gastric diseases to the conditions of the region with a high degree of infection.

It should be noted that when studying the pronounced resistance of HP to clarithromycin by real-time PCR to detect mutations in the A2142G / C, A2143G genes. Of the 30 samples, four were found to have A2142G / C mutation (13.3%). The A2143G mutation was not detected in the samples studied. Consequently, the results were below the 15% limit set by the Maastricht Agreement. Control tests after eradication therapy showed that in the standard triadotherapy group, its effectiveness was 72.5%, which is significantly lower than the required threshold for a satisfactory effect. In contrast, in the group of patients with quadritherapy, HP eradication was observed in 95% of cases. According to modern requirements, the permissible lower threshold for the effectiveness of eradication schemes is > 80%. In the course of the study, depending on the regional characteristics of infection, the effectiveness of triadotherapy averaged 72.5%. Carrying out a modified quadritherapy with the inclusion of BTD in the arsenal of treatment led to a statistically significant increase in the eradication efficiency up to 95%.

Thus, the interpretation of the results obtained indicates that Uzbekistan is a region with a high degree of HP infection of the population. At the same time, 84% of the population of Uzbekistan have a mixed IceA1 / IceA2 genotype CagA HP. In patients with gastric ulcer, the pathogenic strain CagA + VacA s1, VacA m2, IceA 1,2 prevails. For patients with chronic type B gastritis, the prevalence of Cag + VacA s1, VacA m2 and IceA 1 strains is characteristic. The level of resistance of HP strains to clarithromycin averages 13.3%. Carrying out standard triadotherapy is not highly effective, therefore, it is advisable to use quadritherapy with the inclusion of BTD in the therapeutic arsenal.

4. CONCLUSIONS

1. The study of the epidemiological aspects of the prevalence of HP in Uzbekistan indicates a high degree of infection of the population of HP, which is on average 84% in the country;
2. Among the infected population of Uzbekistan, the frequency of detection of the pathogenic strain of HP - CagA + is up to 80% and is typical for patients with HP associated gastric contamination;
3. Due to the presence of HP resistance to clarithromycin in 13.3% of cases and taking into account the low effectiveness of triadotherapy (72.5%), it is advisable to use quadritherapy with the inclusion of BTD in the standard of treatment, which contributes to an increase in the eradication efficiency up to 95%.

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