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Helicobacter Pylori Infection and Its Importance in the Development of Idiopathic Thrombocytopenic Purpura

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HELICOBACTER PYLORI INFECTION AND ITS IMPORTANCE IN THE DEVELOPMENT OFIDIOPATHIC THROMBOCYTOPENIC PURPURA

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Helicobacter Pylori (HP) infection has been associated with chronic inflammation of the stomach and may also be associated with Idiopathic thrombocytopenic purpura (ITP).

A literature review was conducted on the reported research of HP infection associated with ITP.

Key words. Helicobacter Pylori, Idiopathic thrombocytopenic purpura, peptic ulcer, chronic gastritis, gastric B cell lymphoma, hemostasis, autoimmune, hematological pathologies, gastric atrophy, platelets, gastric cancer.

HELICOBACTER PYLORI ИНФЕКЦИЯСИ ВА УНИ ИДИОПАТИК ТРОМБОЦИТОПЕНИК ПУРПУРА РИВОЖЛАНИШИДАГИ АҲАМИЯТИ

Helicobacter pylori (HP) инфекцияси ошқозоннинг сурункали яллиғланиши ва ибиопатик тромбоцитопеник пурпура (ИТП) билан боғлиқ бўлиши мумкин. HP инфекциясини ўрганиш ва ИТП ривожланишига HP инфекциясининг таъсир механизми бўйича илмий адабиётлар ўрганилди.

Калит сўзлар: Helicobacter Pylori, идиопатик тромбоцитопеник пурпура, ошқозон яраси, сурункали гастрит, ошқозоннинг В-хужайрали лимфомаси, гемостаз, аутоиммун касалликлар, гемотологик патологиялар, ошқозон атрофияси, тромбоцитлар, ошқозон саратони.

ИНФЕКЦИЯ HELICOBACTER PYLORI И ЕЕ ЗНАЧЕНИЕ ВРАЗВИТИИ ИДИОПАТИЧЕСКОЙТРОМБОЦИТОПЕНИЧЕСКОЙ ПУРПУРЫ

Инфекция Helicobacter Pylori (HP) связана с хроническим воспалением желудка и может также быть связана с идиопатической тромбоцитопенической пурпурой (ИТП).Был проведен обзор научной литературы по исследованию инфекции HP и механизм влияния HP-инфекции на развитие ИТП.

Ключевые слова: Helicobacter Pylori, идиопатическая тромбоцитопеническая пурпура, язвенная болезнь желудка, хронический гастрит, В-клеточная лимфома желудка, гемостаз, аутоиммунные заболевания, гематологические патологии, атрофия желудка, тромбоциты, рак желудка.

Introduction. Helicobacter pylori infection is a recently re-examined gram-negative bacteria that are radically changing the understanding of the pathogenesis of peptic ulcer disease and, consequently, its treatment [1]. Since Helicobacter pylori infection is related to many gastrointestinal diseases including peptic ulcer, chronic active gastritis, gastric B cell lymphoma and gastric cancer [2,3].

Helicobacter pylori (H. pylori) is a gram-negative, spiral-shaped, flagellated, microaerophilic bacillus that colonizes the gastric mucosa and is likely transmitted via the fecal–oral, or oral–oral route during childhood [4–10]. Prevalent in more than half of the world's population, H. pylori infection occurs more frequently in developing nations [4,5,7]. There are documented differences in virulence factors between Western and East Asian strains of H. pylori, with the Eastern Asian strains suspected to have higher pathogenicity in relation to gastritis and gastric carcinoma [11,12]. Helicobacter pylori is recognized as a causative agent for a variety of gastric diseases, including gastritis, peptic ulcer, and gastric atrophy, and is correlated with an increased risk for gastric cancer [13]. The bacterium has also been linked to several extra-gastric diseases including nutritional deficiencies, such as vitamin B12 deficiency, and hematological pathologies, such as idiopathic thrombocytopenic purpura (idiopathic immune-mediated thrombocytopenia, ITP) [14,15].

Helicobacter pylori infection (HP), causing chronic inflammation of the stomach, is accompanied by the production of cytokines, signaling molecules, which causes activation of pro-inflammatory proteins and promotes intracellular mutations not only locally, but also causes some systemic effects and may affect other organs and systems [1,2]. Numerous studies suggest a possible importance of the HP infection in the development of several gastrointestinal diseases [3, 16]. The list of these diseases is quite extensive, and in the genesis of some of them the role of HP infection can be regarded as proven, in others it is associated with only a part of the cases.It is sometimes assumed the genesis role, but the available scientific data are contradictory, and therefore, require further clarification. It is important to emphasize here that extragastric symptoms usually develop after years from the date of the HP-associated gastritis, they can co-exist with it, but sometimes are very long-term consequences of HP infection. The severity of manifestations of extragastricdisorders initiated by HP does not correspond to the severity of gastroduodenal pathology. In most cases, extragastric manifestations of chronic gastritis activity is quite low, but to localize it usually has a common character with the involvement of the corpus.

It is well known that seropositivity for Helicobacter Pylori infection among healthy people in the population varies considerably from country

to country. This means that the number of people who are carriers of Helicobacter Pylori infection decreased over the past decades in the industrialized countries, and that it increases with age.

According to most studies, on the different series of patients, most of the authors have found a high prevalence of Helicobacter Pylori infection in patients with idiopathic thrombocytopenic purpura. According to the authors, most previous studies involving a fairly large number of patients have been conducted in Italy and Japan. It has been studied that in these countries the prevalence of Helicobacter Pylori infection in healthy population is high (> 70% over the age of 50 years) [5,6], so the prevalence of Helicobacter Pylori infection in patients with idiopathic thrombocytopenic purpura in these countries cannot be given than among the healthy population.

For the first time the assumption of the association between HP infection and ITP infection was made by A. Gasbarrini et al., who reported an increase in the number of platelets in a patient with ITP after HP eradication [19]. Since a report by *Gasbarrini* et al. in 1998, an accumulating body of evidence has proposed a pathophysiological link between ITP and chronic *Helicobacter pylori* (*H. pylori*) infection. Clinical reports have described a spontaneous resolution of ITP symptoms in about 50% of chronic ITP patients following empirical treatment of *H. pylori* infection, but response appears to be geography dependent. Subsequently, this relationship was confirmed by the detection of antibodies to HP and the positive results of respiratory urease test in 70-85% of patients with ITP [8]. G. Emilia et al. [9] showed a 50% efficiency of HP eradication treatment of patients withITP. After successful eradication of HP, most patients show a significant decrease in the level of anti-platelet antibodies (AT-IgG).In the paper T. Ando et al. [10], the platelet count was normalized, after successful eradication was achieved in 67% of patients, while without HP eradication therapy none of the patients has improvement. It is important that the effect of eradication therapy has a long-term nature and is accompanied by a further increase of the number of platelets to the rules after the end of treatment, and it is saved for at least 2 years and does not require any further treatment. T. Ando et al. [22] compared the features of the HP strains in patients with peptic ulcer and non-ulcer dyspepsia and in patients with ITP, and found no significant difference in the detection rate of the main factors of HP pathogens such as CagA, VacA, iceA and hpyIIIR/hrgA. However, they noted the same type of chronic nature of HP-associated gastritis in all patients with ITP, which is characterized by predominant involvement of the gastric body and inflammation activity was similar to that of patients with gastric ulcer.

The mechanism of HP infection influence on the development of ITP is not completely clear. Some authors show the direct effect of HP on platelet function, particularly M. Byrne et al. [23]. He showed that HP is able to bind von Willebrand factor and interact with glycoprotein Ib, inducing platelet aggregation. However, given that the other categories of patients (with peptic ulcer disease, chronic gastritis), platelet count before and after eradication does not change, therefore it is unlikely we are talking about the direct influence of HP on platelets. Most likely, HP induces the formation of antiplatelet autoantibodies by chronic immunologic stimuli arising from chronic inflammation or with HP some antigenic similarity and platelets in a certain category of patients. However, not only NO, but a variety of viral infections may be cause of ITP, including Epstein-Barr virus (EBV). However, in this case ITP usually has an acute rather than a chronic condition [24]. Perhaps the coexistence of two chronic infections (HP + EBV) may be more likely to be realized in the chronic ITP in genetically predisposed subjects. T. Suzuki et al. found that the genotype of TGF-b (G / G or G / A) may predispose to an increase in platelet count after eradication of HP [25,26].

Conclusion. Describing the reasons for ITP as a whole, we can conclude that HP infection is a factor of development in some patients with ITP. Therefore, probably, ITP can be divided into 2 categories: HP-associated and independent. All patients with ITP should be evaluated for HP (serologically or by using breath test), and upon detection of HP its eradication should be considered as the first stage of treatment. If the effect of the eradication is positive the further treatment of ITP is not required. In cases the absence of effect it is advisable to appoint pathogenic therapy of ITP.

References.

1. Gasbarini A, Franceshi F. Autoimmune diseases and Helicobacter pylori infection. Biomed pharmacotheraphy 1999; 53:223-6
2. Tsang KW, LamSK. Helicobacter pylori and extra-digestive diseases. J Gastroenterol Hepatol 1999; 14:844-50.
3. Parsonnet J, HansenS, RodrigesI, GelbAB, WarnkeRa, JellumE, et.al. Helicobacter pylori infection and gastric lymphoma. N Engl J Med1994; 330:1267-71
4. Frydman GH, Davis N, Beck PL, Fox JG. Helicobacter pylori Eradication in Patients with Immune Throm-

bocytopenic Purpura: A Review and the Role of Biogeography. Helicobacter. 2015;20(4):239-251. doi:10.1111/hel.12200
5. Rothenbacher D, Brenner H. Burden of Helicobacter pylori and H. pylori-related diseases in developed countries: recent developments and future implications. Microbes Infect. 2003; 5:693–703. [PubMed] [Google Scholar]
6. Rothenbacher D, Winkler M, Gonser T, Adler G, Brenner H. Role of infected parents in transmission of Helicobacter pylori to their children. Pediatr Infect Dis J. 2002; 21:674–9. [PubMed] [Google Scholar]
7. Frenck RW, Jr, Clemens J. Helicobacter in the developing world. Microbes Infect. 2003; 5:705–13. [PubMed] [Google Scholar]
8. Malaty HM, El-Kasabany A, Graham DY, Miller CC, Reddy SG, Srinivasan SR, Yamaoka Y, Berenson GS. Age at acquisition of Helicobacter pylori infection: a follow-up study from infancy to adulthood. Lancet. 2002; 359:931–5. [PubMed] [Google Scholar]
9. Parsonnet J, Shmuely H, Haggerty T. Fecal and oral shedding of Helicobacter pylori from healthy infected adults. JAMA. 1999; 282:2240–5. [PubMed] [Google Scholar]
10. Zou QH, Li RQ. Helicobacter pylori in the oral cavity and gastric mucosa: a meta-analysis. J Oral Pathol Med. 2011; 40:317–24. [PubMed] [Google Scholar]
11. Higashi H, Tsutsumi R, Fujita A, Yamazaki S, Asaka M, Azuma T, Hatakeyama M. Biological activity of the Helicobacter pylori virulence factor CagA is determined by variation in the tyrosine phosphorylation sites. Proc Natl Acad Sci USA. 2002; 99:14428–33. [PMC free article] [PubMed] [Google Scholar]
12. Shiota S, Matsunari O, Yamaoka Y. Relationship between J-Western CagA subtype and the vacA m2 region of Helicobacter pylori. J Clin Microbiol. 2010; 48:3033–4. [PMC free article] [PubMed] [Google Scholar]
13. Fox JG, Wang TC. Inflammation, atrophy, and gastric cancer. J Clin Invest. 2007; 117:60–9. [PMC free article] [PubMed] [Google Scholar]
14. Franceschi F, Zuccala G, Roccarina D, Gasbarrini A. Clinical effects of Helicobacter pylori outside the stomach. Nat Rev Gastroenterol Hepatol. 2014; 11:234–42. [PubMed] [Google Scholar]
15. Roubaud BC, Franceschi F, Salles N, Gasbarrini A. Extragastric diseases and Helicobacter pylori. Helicobacter. 2013;18(Suppl 1):44–51. [PubMed] [Google Scholar]
16. De Lius DA, Varea C, de la Calle H. Helicobacter pylori infection is markedly increased in patients with autoimmune atrophic thyroiditis. J Klin Gastroenterol 1998; 26:259-63
17. Asaka M, Kimura T, Kudo M, TakedaH, MiyazakiT, MikiK, Graham DY. Relationship between Helicobacter Pylori to serum pepsinogen in an asymptomatic Japanese population. Gastroenterology1992; 102:760-6.
18. Ruso A, EboliM, PizettiP, Di Felice G, RavagniniF, SpinelliP. Determination of Helicobacter pylori infection seroprevalence among Italian blood donors. Eur J Gastroenterol Hepatol 1999; 11:867-73.
19. Gasbarrini A, Franceschi F, Tartaglione R et al. Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. Lancet 1998; 352: 878.
20. Grimaz S, Damiani D, Brosolo P et al. Resolution of thrombocytopenia after treatment for Helicobacter pylori: a case report. Haematologica 1998; 84: 283–4.
21. Emilia G, Longo G, Luppi M et al. Helicobacter pylori eradication can induce platelet recovery in idiopathic thrombocytopenic purpura. Blood 2001; 97: 812–4.
22. Ando T, Tsuzuki T, Mizuno T et al. Characteristics of Helicobacter pylori-induced gastritis and the effect of H. pylori eradication in patients with chronic idiopathic thrombocytopenic purpura. Helicobacter 2004; 9: 443–52.
23. Byrne MF, Kerrigan SW, Corcoran PA et al. helicobacter pylori bind von Willebrand factor and interacts with GPIb to induce platelet aggregation. Gastroenterology 2003; 123: 1846–54.
24. Jenson HB. Acute complications of Epstein-Barr virus infectious mononucleosis. Curr Opin Pediatr 2000; 12: 263–8.
25. Suzuki T, Matsushima M, Shirakura K et al. Association of inflammatory cytokine gene polymorphisms with platelet recovery in idiopathic thrombocytopenic purpura patients after the eradication of Helicobacter pylori. Digestion 2008; 77: 73–8.
26. Recommendations of the American Society of Hematology. Ann Intern Med 1997;1x:319—326.