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Relationship between Helicobacter Pylori Infection and Immune Thrombocytopenic Purpura and the impact of treatment; review article

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Abstract

Helicobacter pylori infection is one of the most prevalent bacterial infections worldwide, impacting up to 50% of the global population. Various diagnostic methods, both invasive and noninvasive, have identified this infection, which has been linked to numerous disorders, both within the stomach and beyond. Immune thrombocytopenic purpura (ITP) is one such extra-gastric condition associated with H. pylori, and diagnosing it involves excluding other potential causes of low platelet counts, which can be distressing. In specific instances, H. pylori infection plays a role in the progression of the disease through diverse mechanisms, including molecular mimicry, an elevation in plasmacytoid dendritic cells, and a unique immune response by the host to virulence factors such as vacuolating-associated cytotoxin gene A (VacA) and cytotoxin-associated gene A (CagA). Eradicating H. pylori has shown benefits in treating some ITP patients, making it advisable to include screening programs in the evaluation of ITP patients.

Keywords: H pylori, ITP, Molecular Mimicry, Extra-Gastric.

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العلاقة بين عدوى الجرثومة البوابية الملتوية و وفرفرية قلة الصفيحات المناعية وتأثير العلاج، مقالة مرجعية

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المستخلص

تعد عدوى الجرثومة البوابية الملتوية واحدة من أكثر أنواع العدوى البكتيرية انتشارًا في جميع أنحاء العالم، حيث تصيب ما يصل إلى 50٪ من سكان العالم. العديد من الطرق التشخيصية، الباضعة وغير الباضعة، تستخدم للتعرف عليها، وتم ربطها بالعديد من الامراض، سواء داخل المعدة أو خارجها. فرفرية نقص الصفيحات المناعية هي إحدى الامراض خارج المعدة المرتبطة بها، وتشخيصها يتضمن استبعاد الأسباب المحتملة الأخرى لانخفاض عدد الصفائح الدموية، والتي يمكن أن تكون مجهدة. في حالات محددة، تلعب عدوى الجرثومة البوابية الملتوية دورًا في تطور المرض من خلال آليات متنوعة، بما في ذلك المحاكاة الجزيئية، وارتفاع الخلايا المتغصنة البلازمية، والاستجابة المناعية الفريدة من قبل المضيف لعوامل الشراسة مثل جين السموم الخلوية المرتبطة بالفجوات نوع A (VacA) والجين المرتبط بالسموم الخلوية نوع A (CagA). لقد أظهر القضاء على هذه الجرثومة فوائد في علاج بعض مرضى فرفرية قلة الصفيحات المناعية، مما يجعل من المستحسن تضمين برامج التحري عن هذه البكتريا في متابعه هؤلاء المرضى.

الكلمات المفتاحية: الجرثومة البوابية الملتوية، فرفرية قلة الصفيحات المناعية، المحاكاة الجزيئية، خارج المعدة

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Introduction

Helicobacter pylori infection

Helicobacter pylori infection persists as one of the dominant bacterial infections globally, with extensive research demonstrating its ongoing high occurrence in the majority of nations. Approximately one-third of individuals in North

European and North American populations continue to harbor H. pylori, whereas in other parts of Europe, the Americas, and Asia, the infection affects more than 50% of the population[1].

This is a gram-negative bacterium with a spiral shape, flagella, and a preference for low oxygen levels. Its primary habitat is the human stomach, and it possesses microbiological characteristics that enable it to survive in challenging conditions, including the acidic environment of the stomach [2,3].

The exact method of transmission remains uncertain. Epidemiological research has indicated that the most common routes are through oral-oral, fecal-oral, or gastro-oral contact. Nevertheless, stomach contamination with H. pylori could occur if food comes into contact with water or soil that is contaminated with the bacterium [4].

Several diagnostic techniques have been devised to identify this infection, and achieving precise diagnoses in clinical settings requires tests with sensitivities and specificities exceeding 90%. These tests can be broadly categorized into two groups: invasive and noninvasive diagnostic approaches. Invasive methods involve procedures like endoscopic imaging, histology, rapid urease tests, culture, and molecular tests. Noninvasive options include urea breath tests, stool antigen tests, serological assessments, and molecular testing, which have proven to be particularly valuable [5].

Common symptoms include nausea, vomiting, burping, and loss of appetite. Additional signs include of frequent burping, bloating, weight loss, and heartburn [6].

Recent studies have linked this infection to a range of medical conditions, including the onset of neurological, dermatological, hematological, cardiovascular, ophthalmic, metabolic, hepatic, and allergic disorders[7].

Significant blood-related disorders associated with this infection comprise mucosa-associated lymphoid tissue lymphoma (MALT), idiopathic thrombocytopenic purpura, as well as vitamin B12 and iron deficiencies. Eliminating H. pylori infection may assist in managing these conditions [8].

There is no universally agreed-upon treatment approach for H. pylori infection. Nevertheless, all these approaches focus on alleviating symptoms and repairing the mucosal damage caused by the infection [7].

The conventional triple treatment regimen, which includes clarithromycin, amoxicillin, or metronidazole for a seven-day duration, has shown an initial treatment success rate of only 73%. According to German guidelines, the standard triple therapy should extend from 7 to 14 days, and quadruple therapy involving bismuth or triple therapy with a fluoroquinolone should last for 10 days [9].

Immune Thrombocytopenic Purpura

The hematological disorder referred to as immune thrombocytopenia (ITP) is characterized by immune-driven platelet reduction and varying levels of bleeding. ITP is typically an acquired condition, with an occurrence rate of 3.3 cases per 10,000 people in Europe [10].

ITP is classified into three categories: acute, persistent, and chronic. Acute ITP commonly occurs in children, lasting around three months, and often spontaneously resolves without any treatment. Chronic ITP, on the other hand, persists for a duration of three to twelve months. When thrombocytopenia is consistently present for at

least a year, primarily in adult patients, it is referred to as chronic ITP [11,12].

Apart from dry or wet purpura, fatigue serves as a symptom and a warning sign. While many individuals may experience mild or minimal symptoms, severe and potentially life-threatening bleeding can still occur [13].

Diagnosing it still relies on ruling out other potential reasons for thrombocytopenia, which can be distressing because the investigation should ideally uncover no underlying cause for the low platelet count[13]. The origin of the thrombocytopenia remains uncertain[14].

Although there are yet unexplored aspects in the development of ITP, the primary pathophysiological mechanism centers on the production of IgG antibodies against platelet surface proteins, particularly GPIIb-IIIa and GIb-IX. Additionally, ITP may be linked to H. pylori infection and infections caused by other microorganisms [11].

Extensive research has been conducted on Rituximab, eltrombopag, avatrombopag, and romiplostim, and high-dose dexamethasone can be considered as an effective alternative to prednisone. Currently, splenectomy is recommended only if medicinal treatments have proven ineffective, and this decision takes into account the patient's age and concurrent health conditions[15]. In specific cases, intravenous high-dose immunoglobulins (IVIg) may be used as an initial treatment, especially for individuals at high risk of bleeding. In some cases, both immunoglobulins and corticosteroids may be given together to expedite the rise in platelet levels[10].

How H. Pylori infection is linked to ITP

Prior studies have suggested various mechanisms through which H. pylori induces its effects, such as molecular mimicry, the elevation of plasmacytoid dendritic cells, and the host's immune responses to virulence factors injected into host gastric epithelial cells, such as vacuolating-associated cytotoxin gene A (VacA) and cytotoxin-associated gene A (CagA) [14]. Antibodies generated against H. pylori antigens, like cytotoxin-associated gene A (CagA), engage with multiple glycoprotein antigens (GP IIb/IIIa, GP Ib/IX, and GP Ia/IIa) situated on the surface of platelets. Another proposed theory for this connection suggests that the bacteria hinder Fc receptors on monocytes in the peripheral blood, leading to increased anti-platelet antibodies and a rise in platelet turnover due to reduced FcRIIB production. In response to the infection, a Th1 T-cell response generates IL-2 and interferon gamma. Interaction with H. pylori results in uncontrolled growth and proliferation of B-lymphocytes, primarily CD5+ B-cells. These cells produce IgM and IgG3 antibodies, which exhibit polyreactivity and auto-reactivity[16].

In regions where it's relevant, the initial evaluation should involve diagnosing Helicobacter pylori through either the urea breath test or the stool antigen test (evidence level IIa; Grade B recommendation)[15].

ITP patients are presently recommended to contemplate an eradication treatment, involving a two-week regimen of triple therapy that combines Proton pump inhibitors (such as omeprazole, lansoprazole, pantoprazole) with antibiotics like amoxicillin, clarithromycin, and metronidazole for a lasting solution [11].

Discussion

Numerous studies have confirmed the connection between H. pylori infection and ITP, as well as the advantages of eradication therapy in treating ITP patients. A review performed by Takushi and team came to the consensus that, aligning with international guidelines, including those from Japan, chronic ITP is viewed as an extragastric manifestation of H. pylori infection. Consequently, the recommended approach involves eradication therapy, with documented instances of platelet count improvement post-treatment, known as responders, observed in various countries[12].

Following systematic reviews and meta-analyses in line with PRISMA guidelines, a separate study suggests that the implicated mechanisms involve the increased production of plasmacytoid dendritic cells, whose projections activate the host's immune response, leading to the generation of various interleukins. These mechanisms include disturbances in phagocytosis due to heightened monocyte activity and the reduced expression of FcRIIB receptors. Furthermore, the presence of von Willebrand factor (vWf) and anti-H. pylori IgG on the surfaces of various H. pylori strains leads to the activation and grouping of platelets.

Antibodies produced against the virulent factor CagA and the interaction between VacA and multimerin-1 on platelet surfaces play a role in the development of thrombocytopenic purpura, prompting the host's immune system to react.. Similar to this, ITP patients who experience a significant increase in platelet count compared to their pre-treatment baseline have demonstrated the efficacy of H. pylori eradication therapy (triple therapy) [11].

A study conducted by Kwuana and colleagues found that in regions where H. pylori infection is prevalent, such as Japan, there is a growing recognition of the importance of identifying and treating H. pylori in patients who appear to have typical ITP. An increasing body of research indicates that the subset of ITP linked to H. pylori differs from other ITP subsets, emphasizing the bacterium's crucial role in the disease's development [17].

A study conducted by Frydman and colleagues proposed a potential new diagnostic and therapeutic strategy for patients with unexplained hematological disorders. This strategy takes into consideration the noteworthy pathological interaction between infectious agents such as H. pylori and ITP, while also factoring in the impact of genetic diversity and geographic elements[14].

An Iraqi study carried out by the National Center of Hematology at Al-Mustansiriya University validated the existence of this association [18]. Another study conducted at Al Kadhimiah Teaching Hospital in Iraq concluded that H. pylori infection may potentially be a cause of idiopathic thrombocytopenic purpura. Eliminating this infection can serve as a treatment, especially in cases that are chronic and challenging to manage. For the detection of H. pylori infection in children with idiopathic thrombocytopenic purpura, the ELISA test can be employed as a screening method [19].

Conclusions

H. pylori infection is widespread and is associated with ITP, which can be regarded as one of its extragastric manifestations. Eradicating H. pylori has shown benefits in treating ITP patients. Therefore, it is recommended to screen for H. pylori infection in individuals with ITP.

References

[1] . Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of Helicobacter pylori infection. Helicobacter. 2014 Sep;19

[2] . FitzGerald R, Smith SM. An Overview of Helicobacter pylori Infection. Methods Mol Biol. 2021;2283:1-14.

[3] . Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M. Helicobacter pylori and extragastric diseases: A review. World J Gastroenterol. 2018 Aug 7;24(29):3204-3221.

[4] . Yang JC, Lu CW, Lin CJ. Treatment of Helicobacter pylori infection: current status and future concepts. World J Gastroenterol. 2014 May 14;20(18):5283-93.

[5] . Wang YK, Kuo FC, Liu CJ, Wu MC, Shih HY, Wang SS, Wu JY, Kuo CH, Huang YK, Wu DC.Diagnosis of Helicobacter pylori infection: Current options and developments. World J Gastroenterol. 2015 Oct 28;21(40):11221-35.

[6] . Sharndama HC, Mba IE. Helicobacter pylori: an up-to-date overview on the virulence and pathogenesis mechanisms. Braz J Microbiol. 2022 Mar;53(1):33-50.

[7] . de Brito BB, da Silva FAF, Soares AS, Pereira VA, Santos MLC, Sampaio MM, Neves PHM, de Melo FF. Pathogenesis and clinical management of Helicobacter pylori gastric infection. World J Gastroenterol. 2019 Oct 7;25(37):5578-5589.

[8] . Goderska K, Agudo Pena S, Alarcon T. Helicobacter pylori treatment: antibiotics or probiotics. Appl Microbiol Biotechnol. 2018 Jan;102(1):1-7.

[9] . Fischbach W, Malfertheiner P. Helicobacter Pylori Infection. Dtsch Arztebl Int. 2018 Jun 22;115(25):429-436.

[10] . Vianelli N, Auteri G, Buccisano F, Carrai V, Baldacci E, Clissa C, Bartoletti D, Giuffrida G, Magro D, Rivolti E, Esposito D, Podda GM, Palandri F. Refractory primary immune thrombocytopenia (ITP): current clinical challenges and therapeutic perspectives. Ann Hematol. 2022 May;101(5):963-978.

[11] . Ihtesham A, Maqbool S, Nadeem M, Bilawal Abbas Janjua M, Sundus O, Bakht Naqqash A, Inayat Mohamed W, Turab Haider S, Ahmad M, Ahmad Talha Mustafa M, Osama Mehboob H. Helicobacter pylori induced Immune Thrombocytopenic Purpura and perspective role of Helicobacter pylorieradication therapy for treating Immune Thrombocytopenic Purpura. AIMS Microbiol. 2021 Sep 2;7(3):284-303.

[12] . Takeuchi H, Okamoto A. Helicobacter pyloriInfection and Chronic Immune Thrombocytopenia. J Clin Med. 2022 Aug 17;11(16):4822.

[13] . Provan D, Semple JW. Recent advances in the mechanisms and treatment of immune thrombocytopenia. EBioMedicine. 2022 Feb;76:103820.

[14] . Frydman GH, Davis N, Beck PL, Fox JG. Helicobacter pylori Eradication in Patients with Immune Thrombocytopenic Purpura: A Review and the Role of Biogeography. Helicobacter. 2015 Aug;20(4):239-51.

[15] . Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, Ghanima W, Godeau B, González-López TJ, Grainger J, Hou M, Kruse C, McDonald V, Michel M, Newland AC, Pavord S, Rodeghiero F, Scully

M, Tomiyama Y, Wong RS, Zaja F, Kuter DJ. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019 Nov 26;3(22):3780-3817.

[16] . Hasni S, Ippolito A, Illei GG. Helicobacter pylori and autoimmune diseases. Oral Dis. 2011 Oct;17(7):621-7.

[17] . Kuwana M. Helicobacter pylori-associated immune thrombocytopenia: clinical features and pathogenic mechanisms. World J Gastroenterol. 2014 Jan 21;20(3):714-23.

[18] . Baan A. Mtashar, Zeyad A. Shabeeb, Zainab F.Ashoor, H.Pylori Associated with Immune Thrombocytopenic Purpura Iraq Joural of Hematology , 2014, Volume 3, Issue 1, Pages 42-46.

[19] . Abbas SS, Hadi TM. The Relationship Between Helicobacter Pylori Infection And Childhood Idiopathic Thrombocytopenic Purpura. JFacMedBagdad [Internet]. 2007 Jul. 1 [cited 2023 Oct. 10];49(2):257-60.