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Current status of Helicobacter pylori association with haematological and cardiovascular diseases: A mini review

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REVIEW ARTICLE

Current status of Helicobacter pylori association with haematological and cardiovascular diseases: A mini review

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Abstract

Helicobacter pylori infection is considered the most commonly prevalent gastrointestinal pathogen where it manages to survive despite the hostile environment of human stomach, leading to various gastric diseases including gastric cancer. Due to the chronic inflammatory state induced by H. pylori and its interaction with host immune system have diverted researchers to investigate its correlation with systemic diseases outside of the gastrointestinal tract. This literature review was done to explore the association of H. pylori infection with haematological and cardiovascular diseases. We used medical subject heading (MeSH) terms "Helicobacter pylori" with "inflammation," "haematological diseases," "coronary heart diseases" or "vascular diseases" to search PubMed database. All relevant studies identified from 2005 to 2015 were included. As many of the studies are small-scale or showed weak association, further studies are needed to address the role of H. pylori in pathogenesis of haematological and cardiovascular diseases.

Keywords: Helicobacter pylori, Iron deficiency anaemia, Thrombocytopenia, Coronary heart disease, Host-immune response.

Introduction

Helicobacter pylori (H. pylori) infects more than 50% of the world's human population and the bacterium is highly adaptive to the gastric mucosa.[1] H. pyloridamages the underlying gastric mucosa and initiate a chronic inflammatory reaction by adhering to the gastric epithelium which further extends gastric tissue injury. H. pylori cytotoxin-associated gene A (CagA) translocation via type IV secretion system into the gastric epithelial cells induces high levels of inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-10 and IL-8.H. pylori infection in the stomach can also affect the development of various diseases outside the stomach by eliciting host immune response against the pathogen binding and chronic inflammation. The H. pylori vacuolating cytotoxin A (VacA) protein can interact with lymphocytes, resulting in blockage of IL-2-mediated T cell proliferation.[2] This lymphocyte inhibition and chronic infection along with the systemic diffusion of various pro-inflammatory cytokines might influence the remote organs and result in extra-gastric inflammatory disease manifestations.

This review was planned to summarise the published literature from 2005 to 2015. We used medical subject headings (MeSH) terms such as "Helicobacter pylori" with "inflammation," "haematological diseases," "Heart diseases" or "vascular diseases" to search PubMed database. All relevant studies identified were included based on study sample size and journal credibility. Studies pertaining to specific disease association related to H. pylori infection were described according to various subheadings as below:

Haematological Diseases

Immune Thrombocytopenia Purpura

Immune thrombocytopenia purpura, also known as idiopathic thrombocytopenic purpura (ITP), is an autoimmune disease defined as isolated low blood platelet count (<100x10^9/L) and an increased risk of mucocutaneous bleeding without any apparent cause.[3] Systemic reviews found no difference in the prevalence of H. pylori in adult ITP to un-infected patients, but the prevalence of H. pylori in children with ITP varied widely among different populations.[4,5] First report on H. pylori association with haematological disorders, such as ITP, was described over two decades ago. Since then several studies from places such as Turkey, Italy and Japan had reported cases of patients suffering from ITP showed normalising platelet count after successful eradication of H. pylori.[6,7] A consolidated review of worldwide case series analysed a total of 1410 H. pylori-infected ITP patients out of which 56.9% showed recovery in platelet count to normal after successful H. pylori eradication.[8]

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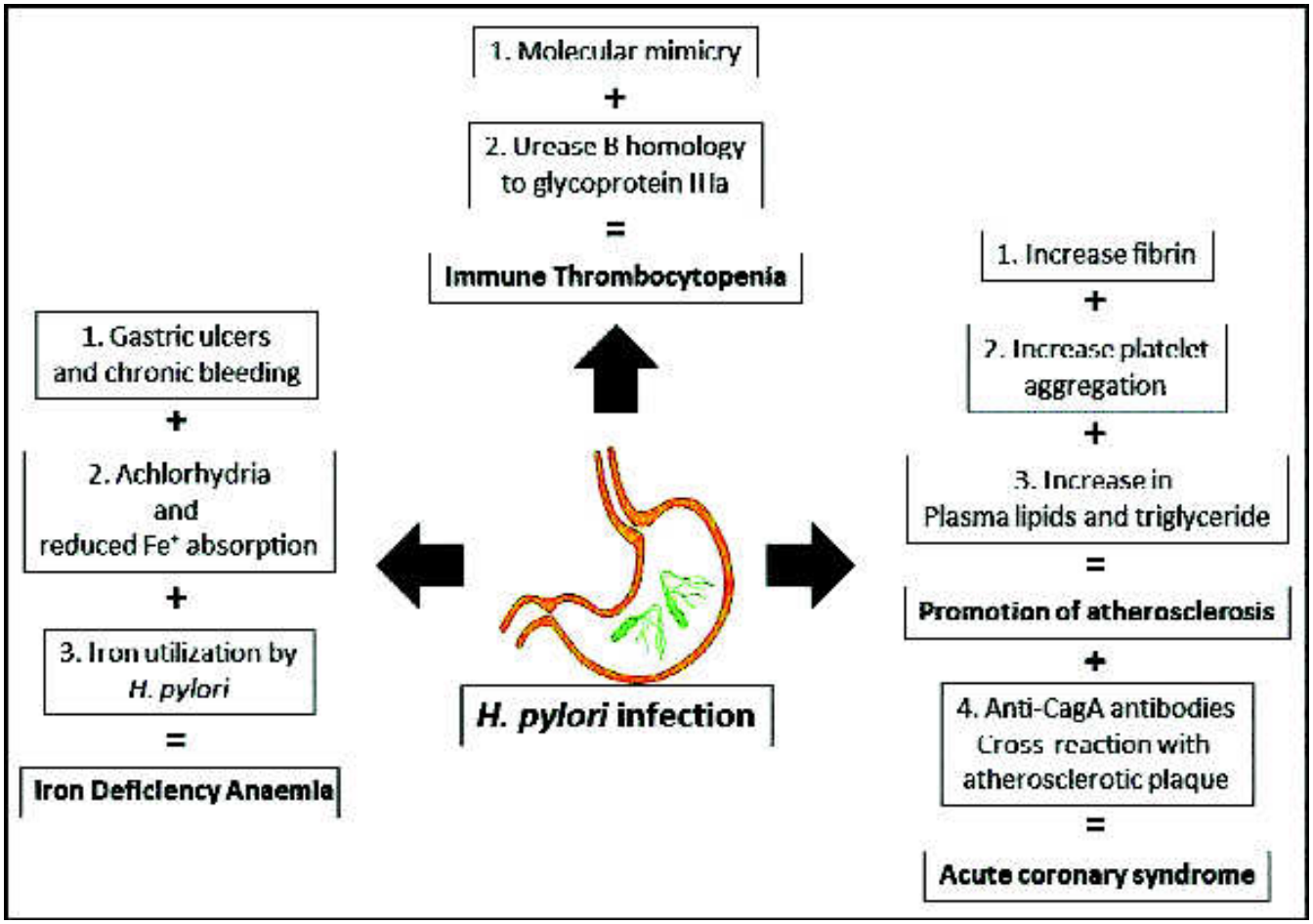

Figure: Pathogenic mechanisms proposed by previous studies to explain the role of Helicobacter pylori in association with haematological and cardiovascular diseases.

Also, another systemic review involving more than 1500 patients reported positive platelet count response following H. pylori eradication.[9] Several hypotheses had been proposed to explain the role of H. pylori in ITP development (Figure). This includes molecular mimicry between antigens and homology of H. pylori Urease B with platelet surface glycoprotein IIIa leading to platelet destruction, but the exact mechanism is not completely understood.[6] These studies so far support detection and eradication of H. pylori as clinically worthwhile approach in all ITP patients. Also, H. pylori eradication in chronic ITP patients has been recommended by the Second Asia-Pacific Consensus Guidelines for H. pylori infection.[10]

Anaemia Due to Iron Deficiency

Iron deficiency anaemia (IDA) is an anaemia caused due to very low levels of body stores of iron leading to impaired erythropoiesis. Peripheral blood smear shows hypochromic, microcytic red blood cells. Iron deficiency is the most common cause of anaemia usually due to nutritional deficiency, severe menstrual blood loss or gastrointestinal bleeding.[11] The role of H. pylori infection in the pathogenesis of iron restricted anaemia is already validated and more than 60% of the patients showed complete recovery from anaemia only after successful H. pylori eradication.[12] A study by Monzon et al. performed on Spanish adults suffering with chronic IDA showed that 38% patients were infected with H. pylori. In those patients, anaemia was resolved and iron levels returned to normal after 6 to 12 months of complete H. pylori eradication.[13] In children, H. pylori infection was associated with low levels of mean corpuscular haemoglobin (MCH) along with lower mean corpuscular value (MCV). In that study, authors also reported that H. pylori infection status was an indicator of low haemoglobin and ferritin levels.[14] Zuberi et al.[15] evaluated and compared levels of haemoglobin, ferritin and vitamin B12 in patients from Civil Hospital, Karachi, undergoing gastrointestinal (GI) endoscopy according to H. pylori infection status. In this study, the authors confirmed that

H. pylori infection was associated with significantly low levels of haemoglobin, ferritin and vitamin B12.[15]

H. pylori might be able to cause iron deficiency by several mechanisms such as increased loss of iron due to active haemorrhage secondary to gastritis, peptic ulcer or gastric cancer; chronic pangastritis resulting in achlorhydria and reduced iron absorption; reduced ascorbic acid or iron utilisation by H. pylori itself for colonisation.[16] However, the exact association of H. pylori with the development of IDA is still not fully understood. Hepcidin, which is released by hepatocytes, is an essential regulator of iron metabolism and an acute phase reactant. Elevated serum levels of hepcidin increases the breakdown of iron transporter protein, ultimately inhibiting iron uptake. Moreover, increased levels of serum pro-hepcidin were reported in H. pylori infected anaemia patients.[17] Furthermore, recent studies also showed that serum hepcidin was elevated in H. pylori-infected patients and the levels were normalised after H. pylori eradication.[18,19]

Other Haematological Associations

Several other haematological diseases had also been associated with H. pylori infection, such as antiphospholipid syndrome, autoimmune neutropenia, mucosa-associated lymphoid tissue (MALT) lymphoma, myelodysplastic syndrome, plasma cell dyscrasias and Schönlein-Henoch Purpura.[8,20] H. pylori infection can stimulate conditioning of polyclonal B lymphocytes and gastric MALT lymphoma formation through antibody production. Although the stomach is normally devoid of mucosal lymphoid tissue, MALT type acquired tissue can develop during chronic H. pylori infection.[21] However, except for the MALT lymphoma, the exact mechanism by which H. pylori is responsible for pathophysiology of these other diseases is still unclear and might be linked to the host response against the bacteria-related factors.

Cardiovascular Diseases

Coronary Heart Disease

Coronary heart disease (CHD), or ischaemic heart disease, is an inadequate blood supply to the myocardial muscles due to narrowing or obstruction of the coronary arteries caused by atherosclerosis plaque formation. Many researchers have investigated epidemiological and pathophysiological relationship between CHD and H. pylori infection. Liu et al. performed a meta-analysis by selecting 26 case-control studies and more than 5,000 myocardial infarction (MI) patients to estimate risk of MI by H. pylori infection. They verified a significant relationship between H. pylori infection and an increased risk of MI, especially in patients of younger age.[22] A retrospective cohort study by Lai et al. randomly selected 17,075 H. pylori-infected participants from Taiwan National Health Insurance Research Database and for the comparison group 68,300 participants from the general population free of H. pylori infection frequency-matched by age, gender, and index year. They demonstrated that H. pylori infection significantly increases the risk of acute coronary syndrome, and the risk of developing coronary syndrome in H. pylori-infected patients increased with the presence of any comorbidity.[23] However, several prospective and case-control studies showed that the association between acute MI and H. pylori infection is confounded significantly by the presence of other risk factors, such as hypertension, diabetes etc.[24] Such heterogeneous and conflicting studies make it difficult to reach a clear conclusion.

H. pylori infection can stimulate leukocytes to release a substance which is able to convert circulating fibrinogen into fibrin, increasing blood coagulation. H. pylori is also able to interact with platelet glycoprotein Ib, L-selectin and P-selectinvia binding to von Willebr and factor, inducing platelet aggregation. Some studies proposed that H. pylori can cause increased thrombogenesis by increasing levels of lipids, triglyceride, TNF and IL-6 in the plasma; subsequently all of these will cause inflammation and promote clot formation at the site of a previous atherosclerotic lesion.[25] The antibodies against H. pylori proteins are capable of recognising host proteins located inside the atherosclerotic plaque triggering an acute coronary syndrome by destabilising an atherosclerotic plaque as a result of inflammation.[26] Also, H. pylori can directly invade macrophages and reach the vascular site away from its primary colonisation site affecting the vascular wall surface and the cytoplasm of endothelial cells, which is evident by the presence of H. pylori deoxyribonucleic acid (DNA) in the atheroma plaques.[27] A study by Rozankovic et al. reported a cross-reaction between anti-CagA antibodies and peptides of atherosclerotic carotid arteries. Furthermore, the anti-CagA antibodies can also recognise antigens located inside the coronary atherosclerotic plaque of patients with CHD.[28] These studies led to a conclusion that the infection by H. pylori CagA-positive strains in patients with classic cardiovascular risk factors increases the risk of acute coronary syndrome.

Other Vascular Diseases

CagA-positive H. pylori infection association with non-cardioembolic ischaemic stroke has also been investigated.[29] A study by Wasay et al.[30] followed a group of patients with H. pylori gastritis over a period of time to identify the risk of non-cardioembolic stroke. In this study,

the gastritis patients with and without H. pylori infection were included from the department of Medicine, Aga Khan University, Karachi. During the two-year follow-up, 3 out of 162 patients (1.85%) with H. pylori-associated gastritis had stroke. Also, hypertension was more commonly seen in H. pylori group.[30] It is possible that H. pylori infection might stimulate an increase in IL-18 levels within carotid artery intima, increasing atherosclerotic susceptibility. Also, H. pylori activates platelets and can affect the coagulation process.[31] Chen et al. in their study, concluded that only a small subclass of patients with non-cardioembolic ischaemic stroke are affected by CagA-positive H. pylori infection.[32] Moreover, many other studies have shown a potential relationship of H. pylori infection in the occurrence of pre-eclampsia, a hypertensive and coagulative disorder.[33] Anti-CagA antibodies are able to recognise β-actin of cytotrophoblast cells and affect their invasiveness.[34] Furthermore, high H. Pylori infection prevalence was observed in patients with migraine; and after complete H. pylori eradication, patients showed considerable clinical improvement.[35]

Conclusion

Studies conducted over the last decade or so fully validated the role of H. pylori in some haematological diseases. Due to these findings, H. pylori eradication is included in the guidelines for the management of ITP and IDA. Therefore, we recommend that physicians should evaluate H. pylori infection status in all patients with haematological diseases and eradication should be performed in positive cases. However, the relationship between H. pylori and cardiovascular diseases is still unclear. A strong link between coronary heart diseases and infection with H. pylori CagA+ strains has been reported, but as CagA is capable of triggering strong host inflammatory response, there is a possibility of induction of atherosclerosis and coronary heart disease due to such chronic inflammatory state. To establish certain role of H. pylori infection in association with cardiovascular diseases, more studies are required. However, the polymorphism in host genetic factors and the geographical diversity of H. pylori strains must be taken into consideration before designing these new studies.

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