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MINIREVIEWS

Current views of the relationship between *Helicobacter pylori* and Henoch-Schonlein purpura in children

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Abstract

Helicobacter pylori (*H. pylori*) is one of the factors involved in the pathogenesis of various gastrointestinal diseases and may play a potential role in certain extra-intestinal diseases. *H. pylori* infection are mainly acquired during childhood, and it has been reported that in endemic areas of China the infection rates are extraordinarily higher in HSP children, particular those with abdominal manifestations. Furthermore, eradication therapy may ameliorate Henoch-Schonlein purpura (HSP) manifestations and decrease the recurrence of HSP. Therefore, results suggested that detection of *H. pylori* infection by appropriate method ought to be applied in HSP children. Current evidences indicate that local injury of gastric mucosa and immunological events induced by *H. pylori* infection are involved in the development of HSP. Increased serum IgA, cryoglobulins, C3 levels, autoimmunity, proinflammatory substances and molecular mimicry inducing immune complex and cross-reactive antibodies caused by *H. pylori* infection might play their roles in the course of HSP. However, there are no investigations confirming the causality between *H. pylori* infection and HSP, and the pathogenesis mechanism is still unclear. More bench and clinical studies need to be executed to elaborate the complex association between *H. pylori* and HSP.

Key words: *Helicobacter pylori*; Henoch-Schonlein purpura; Children

Core tip: This is the first comprehensive review to report current clinical and bench studies focusing on the potential role of Helicobacter pylori infection in Henoch-Schonlein purpura children. We also presented the possible mechanism underlying their association and the questions need to be addressed in the future studies.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative spiral, flagellated and microaerophilic bacterium colonizing human gastric mucosa as a significant factor involved in the pathogenesis of various gastrointestinal diseases. Evidences indicate that this bacteria may participate in certain extra-intestinal disease progression *via* various comprehensive mechanisms[1-3]. Recently, *H. pylori* infection or *H. pylori* induced gastritis was observed to be related to iron-deficiency anemia (IDA)[4-8], and the eradication therapy was reported to be effective in improving ferritin level or even curing IDA[4-12]. Similar relationship between idiopathic thrombocytopenic purpura (ITP), a common hematologic disease in children, and *H. pylori* infection was also revealed by amount of physician-conducted clinical studies[13-18]. In the Asia-Pacific Consensus Guidelines and European Helicobacter and Microbiota Study Group Consensus 2012, it was recommended that eradication of *H. pylori* infection was necessary in certain patients with chronic ITP[19,20]. Furthermore, IDA and ITP were considered to be the extra-intestinal diseases related to *H. pylori* infection confirmed by many clinical trials[4,6-8,21-24]. Several relatively weaker evidences indicated that *H. pylori* infection or its related immune response possibly had interferences with some other extra-intestinal diseases, like cardiovascular, neurological and endocrine disorders[25-30].

H. PYLORI INFECTION AND HENOCH-SCHONLEIN PURPURA

Henoch-Schonlein purpura (HSP) is a common disease in children. It is characterized by IgA-deposits in vessel walls and renal mesangium and defined as acute leukocytoclastic vasculitis of small vessels. Although it is known that the cause of HSP is various, infectious agents are considered as the most important etiological factors[31,32]. Besides the purpura, gastrointestinal manifestations, usually noted as abdominal colic and intra-gastrointestinal hemorrhage, are concomitant during the course of disease and associated with therapeutic strategy and prognosis.

On the other hand, the prevalence of *H. pylori* ranges from 20% to 80%, which makes its infection popular worldwide[33]. Patients get infected predominantly in childhood and persists germ-carrying status mostly through their lifetime[34]. Few infected-individuals will develop upper gastrointestinal disorder, majority of them keep asymptomatic lifelong. Thus many of these children get diagnosed only after other diseases causing intestinal manifestations.

The possible relation between *H. pylori* infection and HSP was firstly enlightened by several cases reports in adults suffering HSP and gastritis simultaneously[35-37]. The *H. pylori* infection could be detected by both ^{13}C-urea breath test. The golden standard of diagnostic relied on gastric mucosal biopsy. Reinauer *et al*[35] reported that in a HSP and chronic gastritis case with diagnosed *H. pylori* infection, the purpura, intestinal symptoms and albuminuria disappeared after eradication treatment. However, the patient was detected to be infected again while the purpura recurred 10 mo later, while the symptoms improved after elimination of *H. pylori*. Mozrzymas *et al*[38] and Mytinger *et al*[39] respectively presented the cases of children with this issue. It was also reported that in children with HSP and duodenal ulcer, purpura manifestations were ameliorated after *H. pylori* eradication was utilized.

Quantity of articles in China reported their investigations on the potential association between *H. pylori* infection and HSP[40-50]. Different from the literatures of cases from Western country, quite a lot of Chinese studies had enough sample sizes to perform cohort study, thus the results might be more reliable. Yuan *et al*[46] reported a retrospective study with the largest sample size, which included 186 HSP patients and 150 control cases. Anti-Hp IgG test was utilized as diagnostic method to detect *H. pylori* infection. Forty point nine percent (76/186) of patients in HSP group and 15.3% (23/150) of controls were confirmed to be infected. Based on the outcomes, the authors concluded that the infection was related to HSP occurrence[46]. In another research with the largest follow-up sample size, Li *et al*[43] claimed that OCA (O: Omeprazole; C: Clarithromycin; A: Amoxicillin) eradication treatment was effective in preventing HSP recurrence in those cases infected by *H. pylori* simultaneously, which were confirmed by rapid urease test (RUT).

A meta-analysis had been made to get the pooled *H. pylori* infection rate and identify the relativity between the two diseases[51]. One thousand three hundred and nine cases, including 749 HSP children and 560 healthy controls were enrolled in the pool analysis. The infection rates among the HSP children showed a wide range, which was from 22% to 75%, while those were only 3% to 44% in the healthy controls. Utilizing the data from 10 studies, the meta-analysis got a conclusion that this bacterial infection was statistically significantly associated to the increased occurrence of HSP with nearly 4 folds of risks in Chinese children (OR = 3.80, 95%CI: 2.54-5.68, $P < 0.001$). This study also claimed that the eradication therapy might play a protective role in the HSP recurrence, based on the data of 4 available studies (RR = 0.38, 95%CI: 0.25-0.58, $P < 0.001$) (Table 1).

It was interesting to see that the infection rate in HSP children reported in China varied in regions, which might be the outcome of combination of the different *H. pylori* infection prevalence and HSP incidence rate. In addition, researcher agreed that there was a geographic

Table 1 Brief view of current clinical control studies that focusing on the relationship between Henoch-Schonlein purpura and *Helicobacter pylori* infection in Chinese children

Ref.	Year	Total	Healthy control	HSP	Gastrointestinal HSP	HP in HSP children (%)	HP in control (%)	Eradication therapy
Wang *et al*[40]	2004	65	30	35	30	22.86	3.33	Yes
Zhang *et al*[41]	2004	120	60	60	-	38.33	23.33	No
Lv *et al*[42]	2005	62	28	34	11	23.53	3.57	No
Li *et al*[43]	2006	270	120	150	90	60.00	44.17	Yes
Chen *et al*[44]	2006	62	28	34	11	23.53	3.57	No
Wang *et al*[45]	2007	98	30	68	36	44.12	6.67	Yes
Yuan *et al*[46]	2007	336	150	186	118	40.86	15.34	Yes
Li *et al*[47]	2008	69	30	39	-	74.36	43.33	Yes
Li *et al*[48]	2008	102	42	60	40	58.33	28.57	Yes
Xia *et al*[49]	2008	67	30	37	37	54.05	23.33	No
Gao *et al*[50]	2009	120	40	80	51	62.50	12.50	No

HSP: Henoch-Schonlein purpura.

variation of *H. pylori* strains varies around the world[52]. Cytotoxin-associated gene A (Cag-A) positive strains was dominant among the isolated East-Asia *H. pylori*, whereas cag-A negative could be identified in up to 20% to 40% strains from Europe or Africa. Cag-A positive *H. pylori* strains from above continent showed differences in the repeating sequences numbers from each other, which resulted in variant abilities to infect the host and cause manifestations[53,54]. Similar status was observed when taking *vacA*, another important virulence of *H. pylori*, into consideration[55,56]. This might be the background of why HSP cases with concurrent *H. pylori* infection were rare in western countries (especially those developed one) but commonly encountered in East-Asia area. Thus, the current foundation of assuming the potential relation between *H. pylori* infection and HSP in Western population might not be that solid as in Eastern population.

The diagnosing method was another part that might influence the practice of exploring such possible relations. All the case reports confirmed bacterial infection with biopsy, which was the gold standard of *H. pylori* infection[35,38,39]. However, only 3 of these cohort studies above applied RUT, which was based on the tissues biopsied using endoscopy[43,45,47]. Five studies diagnosed the infection with urease breath test, the others only adopted serum anti-Hp immunoglobin (IgG mainly) test to identify the diagnosis[40,42,46,48,50]. It was known to all that IgG could be detected in the humoral immune system long after *H. pylori* infection or eradication, thus there might be several false positive cases confounded in the samples.

Another concern was the gastro-duodenoscopic manifestations of HSP. In these patients with obvious abdominal symptoms, endoscopy was considered to be a useful tool to confirm the diagnosis and exclude other surgical emergencies. It was reported that duodenum was the most common site of lesions, other sites like gastric antrum, body and angle, but never cardia or esophagus[57]. Endoscopic findings include Erythema, edema, petechiae, ulcers and other intraluminal lesions consisted of common endoscopic findings of HSP[58]. These manifestations overlapped with those of *H. pylori* infections more or less, thus bacteria detection was crucial in the treatment of certain patients.

It was unable to distinguish the *H. pylori* infection timing during the progression of HSP by using current study evidences. Intestinal manifestations may occur at any period of HSP courses, which would be the clue to detecting the *H. pylori* infection. No evidences were able to clarify whether the patients got infected before or after HSP symptoms appeared. It was reported that anti-*H. pylori* IgG level was relatively higher in HSP patients serum, comparing to that in healthy controls, while it was far from revealing the influence of bacterial infection on this autoimmune disorder[59]. Even clinic studies suggested there was strong relationship between *H. pylori* infection and HSP; researchers could not confirm that bacterial infection triggering the development of HSP. In addition, although HSP could be triggered by other infectious conditions, particular some respiratory infections, the limitation of their retrospective background made it impossible to exclude all the infectious or allergic diseases.

Moreover, there were no uniform criteria or parameters to evaluate the effectiveness of *H. pylori* eradication therapy in treating those HSP children suffering the infection. Because of their retrospective basics, the studies which indicated the effectiveness of eradication therapy in control HSP recurrence were not high quality evidences. Prospective well-designed clinical trials might eliminate the skepticism. Therefore, it was urgent to find out the appropriate diagnosing methods and indicators for detecting *H. pylori* infection. It was also necessary to establish the standard to assess the effectiveness of eradication therapy in HSP children.

BIOLOGIC MECHANISM BENEATH HSP AND *H. PYLORI* INFECTION

It is known to all that pathogenesis of HSP remained unclear. The clinical characteristics of HSP were the consequences of systemic leukocytoclastic vasculitis

with polymeric immunoglobulin A (pIgA), activated complements (C3 or C5) and certain fibrinogen/fibrin deposited in vessel walls, without IgG or IgM deposition. The immune complex between these elements in skin, gut, kidney and other organs resulted in the purpura, intestinal manifestation, nephritis and other relatively rare symptoms. Most investigators agreed that IgA1 was crucial in the progression of HSP[60-62]. Thus it could be speculated that any pathogens that were capable of initiation type Ⅲ allergic reaction with elevating serum IgA1 antibody levels and conducted systematic vasculitis might be indispensable in HSP progression.

H. pylori infection could also be diagnosed in IgA nephropathy patients, which shared several similarities with HSP. High level of serum anti-Hp IgA and disposition of pIgA in glomerular were two significant ones among the characteristics[63]. *H. pylori* infection can cause the incline of the serum levels of IgA, C3 and cryoglobulins, which is deduced to promote the immune complexes formation and increase the risk of HSP occurrence[64]. A study in adult patients revealed that, when compared to healthy controls, anti-Hp IgG levels in the acute phase of HSP and anti-Hp IgA/IgG ratios in the remitting phase were significantly higher[65]. However, there was no solid evidence of bench studies clarifying that whether the immune responses or abnormalities induced by *H. pylori* infection was associated with HSP or responsible for triggering the pathological process of the disease.

H. pylori infection resulted in bacterial invasion into gastric mucosa, which led to the direct damage to the physical barrier. Strong systemic humoral and cellular immune responses might be induced. It was assumed that such immune response might be able to coordinate the cross-talk between the infection of *H. pylori* and certain extra-gastrointestinal diseases, embracing autoimmunity, pro-inflammatory substances and molecular mimicry inducing immune complex and cross-reactive antibodies[66-69]. During the course, Ig A was secreted by the mucosa. Although this antibody was capable of inhibiting the adoption of bacterial antigen, preventing the adhesion and movement of *H. pylori*, and neutralization of toxin[63], the secretion was commonly over-activated.

H. pylori infection prognosis relied on the interaction among variant factors, such as virulence of dominant bacteria strain, host characteristics, and environmental influences. The product of vacuolating toxin gene A (*vacA*) and *cagA* were the main virulence factors of *H. pylori*. The *vacA* and *cagA* alleles, encoding the most important *H. pylori* virulence proteins *VacA* and *CagA*, contribute to the isolation of China and Western countries bacterial strains for the functional polymorphism. Based on the high toxigenicity of Chinese *H. pylori* strains and relatively low toxigenicity of strains in western countries, we hypothesize that *vacA* or *cagA* might participate in the progression of HSP through a complicate and unknown mechanism. Experimental research focusing relationship of *H. pylori* and atherosclerosis indicated that *cagA* antigen mimicry the peptides of vascular wall, which also suggested that *cagA* antibody would damage the endothelium[70]. Another study suggested that *cagA* increased the secretion of IgA1 a dose-/time-dependent manner. Furthermore, it also indicated that *cagA* could promote the underglycosylation of IgA1 in B cells[71].

H. pylori infection also conducted the massive secretion of inflammatory mediators, like interleukin (IL)-6, IL-12, IFN-γ, TNF-α, *etc*. By their complicated interaction network, these cytokines participated in the inflammatory response directly or indirectly. Cellular immune response triggered by the infection was another mechanism that might influence the course of HSP. It was reported that $CD4^+$/Treg cells proliferation was incited by *H. pylori* infected dendritic cells with the mediation of IL-1β, the secretion of which was stimulated by *vacA* and γ-glutamyl transpeptidase[72-74]. However, no significant difference in Treg cell level was identified between HSP patients and healthy controls[75,76]. In contrast, Th17 cells activation was also reported to be a functional part of *H. pylori* induced inflammation, and its concentration was demonstrated to be higher in HSP cases[77]. These results suggested that more details of cellular immune reaction beneath the fact of *H. pylori* infection needed further studies to explore.

Molecular mimicry was another approach of *H. pylori* in inducing autoimmune diseases. For example, human Lewis determinants [Le(x) and/or Le(y)] and H determinants expression could be detected in a majority of isolated *H. pylori* strains. While in some other strains, the detected components changed to Le(a), Le(b) and sialyl-Le(x)[78,79]. All the determinants were located in the O-chain of the surface lipopolysaccharide. In the preliminary researches, it was indicated *H. pylori* could evade host responses and evoke autoantibody responses to Le antigens with the help of certain molecular mimicry. Moreover, one study hypothesize that anti-Le autoreactive antibodies induced by *H. pylori* infection were involved in the progression of autoimmune disorders[80]. However, there is lack of clinical evidences could support this issue till now. The role of molecular mimicry in immune disorders, like HSP, requires further comprehensive analysis of T cells and autoantibodies functions. More functional research and clinical studies may focusing on Le antigens and other components in surface lipopolysaccharide of *H. pylori*.

CONCLUSION

Extra-gastric disorders were important aspects of *H. pylori* infection and diseases-correlated to the progression, which was proved by more and more clinical researches in children. Current studies suggested the latent relationship between the infection and HSP in children. Therefore, detecting *H. pylori* carrying status in HSP children, particular those with abdominal manifestations is indispensable in endemic areas. Diagnostic methods which are able to confirm the current infection situation are recommended to detect existence of *H. pylori* in HSP patients. However, it remained unclear how the

bacterial infection got involved in the progression of HSP. Considering the evaluation of the eradication therapy effectiveness in HSP children with *H. pylori* infection is not available, more robust evidences, such as randomized, placebo-controlled, double-blind large sized studies with appropriate diagnostic methods, would be conducted to reveal the potential association between *H. pylori* and HSP and to judge whether eradication therapy should be applied in those children.

Yet, despite some investigation suggested correlations of *H. pylori* infection with HSP in children, there remained many unanswered questions need to be addressed, which may lead to a further comprehension of *H. pylori*'s role in HSP, and to improve therapeutic and preventative strategies: (1) Latest clinic reports had significant drawbacks of sample size and study method. Large sample sized prospective clinic studies or nation-wide epidemiological studies need to be conducted to confirm the correlation or causality between *H. pylori* infection and HSP; (2) Most of current clinical studies were from Asia, particularly from China. Researchers might need to consider whether *H. pylori* strains with high toxicity differed from those with low toxicity in inducing or exacerbating HSP; (3) Further researches are also required to explore whether *H. pylori* infection is the cause of HSP or just only concurrent infection; (4) It is also necessary to know whether the existence of *H. pylori* induces those abdominal manifestations in HSP progression; (5) Long-term intensive follow-up of HSP recurrence post radical therapy is needed to identify the possible relationship between HSP infection and *H. pylori*, and to see the effect of such treatment on controlling recurrence; (6) Future studies answer that whether endoscopy can be a supplementary diagnostic tool when suspected HSP patient with significant digestive symptoms but no typical purpura; and (7) Basic mechanism of crosslink between the two diseases requests more bench studies to illuminate.

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