HELICOBACTER PYLORI AND EXTRAGASTRIC DISEASES - OTHER HELICOBACTERS

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ABSTRACT

The involvement of Helicobacter pylori in the pathogenesis of extragastric diseases continues to be an interesting topic in the field of Helicobacter-related pathology.

Although conflicting findings have been reported for most of the disorders, a role of *H. pylori* seems to be important especially for the development of cardiovascular and hematologic disorders.

Previously isolated human and animal *Helicobacter* sp. flexispira and *'Helicobacter heilmannii'* strains have been validated using polyphasic taxonomy. A novel enterohepatic helicobacter has been isolated from mastomys and mice, adding to the list of helicobacters that colonize the liver. Genetic targets that may aid the classification of novel *Helicobacter* species have emerged. Animal models of helicobacter-induced gastric- and hepatobiliary diseases have gained insights of mechanisms associated with premalignant transformation

EXTRAGASTRIC DISEASES

Helicobacter pylori (*H. pylori*) infection, although confined to the stomach, induces a strong systemic immune host response. It is therefore plausible that untoward effects of this response may contribute to the development of disease in districts other than the gastrointestinal tract. Unfortunately, demonstration of a causal relationship is rather difficult, since the etiology of most of the disorders in which the organism might be involved is multifactorial, *H. pylori* being, at the best, one of the causative agents; furthermore, the organism is not directly involved, and results of eradication therapy are of difficult interpretation. With these limitations in mind, there are two main fields in which *H. pylori* probably play a role, at least in a subset of patients: clinical manifestations of atherosclerosis, and chronic idiopathic thrombocytopenic purpura. Association with other disorder is much less consistent.

Clinical manifestations of atherosclerosis

Published studies involve several aspects of the relationship between *H. pylori* infection and this disorder: epidemiologic association; pathophysiologic mechanisms; results of eradication therapy. Two case-control studies (1,2) assessing the possible relationship between ischemic stroke and *H. pylori* gave discordant results (however, a significant association with CagA positive strains was detected in the negative report), whereas another study, assessing whether the natural history of infected patients with atherosclerotic stroke differs from that of uninfected ones, was unable to detect differences between infected and non infected patients: once again, a significant association with CagA positive strains was found in this study (3).

Two reports, by McDonald et al (4), and by Shmuely et al (5), focused on the possible relationship between Helicobacter pylori and atherosclerotic changes detectable at ultrasonography: both studies did not find an association; Shmuely et al, however, detected an increased risk for patients with CagA positive strains (this association was not examined in the other study).

Some studies (6-9) examined the possibility that genomic material of *H. pylori* may be present in the context of atherosclerotic plaques: both positive (6,7) and negative (8,9) findings have been reported. It should be kept in mind that techniques of genoma amplification carry a high risk of both false positive and false negative findings.

As far as the possible relationship between infection and coronary artery disease (CAD), two case-control studies (10,11) showed a higher prevalence of infection, whereas no significant difference was found in other reports (12-14). In a large cross-sectional survey (15), an association limited to diabetics was found. Of note, only one of the above reported studies (10) analysed CagA status, showing a significant association with active infection in CAD patients.

Three further studies focused on selected groups: diabetic patients(16), patients with end stage renal failure (17), and young patients (18), failing to detect an association.

An inverse correlation with the occurrence of venous by-pass graft occlusion after coronary artery by-pass surgery has been reported (19): caution is needed in the interpretation of this finding, due to the low number of studied patients and the very high rate of infection in patients without occlusion (82%).

One report examined the effects of eradication therapy on relapses in *H. pylori* positive CAD patients (20): a significant beneficial effect of therapy was reported.

Finally, possible pathophysiologic alterations linking *H. pylori* to cardiovascular disease have been explored in several studies: positive association of the infection with systemic markers of inflammation and/or with platelet or clotting factor activation or serum lipids has been reported (11, 21-23); the same parameters, however, were not found to be significantly associated in the majority of reports (5, 13, 15-17, 18, 20, 24). Interestingly, some negative reports found a positive association of infection with cardiovascular disease. This fact suggests that *H. pylori* may lead to overt atherosclerosis through other mechanisms.

In conclusion, conflicting findings have been reported for a causal role of *H. pylori* in cardiovascular disease. By contrast, uniform positive findings have been obtained in studies taking into account the possible association with CagA positive strains.

Idiopathic thrombocytopenic purpura (ITP) and other hematologic disorders

Although most studies concerning this possible association failed to detect significant differences in the prevalence of infection between patients with or without this haematological disorder, there is little doubt that the administration of eradication therapy to *H. pylori* infected patients causes long-lasting remission in approximately half of them. In published studies, the frequency of remission after treatment ranges from 45% to 74% (25-35). Although treatment seems more efficacious in older subjects, remissions are well documented also in children (36). Indirect evidence for a role of *H. pylori* infection in regulating platelet count, derives from a report showing the development of thrombocythemia after eradication (37). Interestingly, *H. pylori* has been implicated in other piastrininopenic states such as thrombotic thrombocytopenic purpura in patients after bone marrow transplantation (38). There is no established mechanism to explain how this organism, which does not invade the gastric mucosa, could be implicated in the pathogenesis of this immune-based platelet disorder. Several theories including molecular mimicry, platelet aggregation, and immunomodulatory effects of macrolides have been proposed to explain the platelet response to anti-H. pylori therapy. Large randomized-controlled studies enrolling patients from various ethnic backgrounds will be necessary to determine the response rate and mechanism of response and to gain a better understanding of the pathogenesis of ITP (39).

H. pylori infection has ben implicated in other hematologic disorders, such as sideropenic and megaloblastic anemia. The organism may theoretically cause host iron deficiency by directly competing with the host for available iron or by impairing iron uptake as a consequence of atrophy-associated gastric hypochlorhydria. This hypothesis has been confirmed by a study showing an impaired absorption of iron after oral load in infected subjects, and reversion to normal after

eradication (40). The relevance of this effect is probably marginal, however, and may have a clinical expression in the case of limited iron stores associated with reduced iron intake, as shown in animals (41). Indeed, in some situations at risk for iron deficiency anemia, such as pregnancy (42), subtotal gastrectomy (43) and celiac disease (44), an association with infection has been suggested. Results of eradication therapy are not uniform: whereas it was found ineffective in Bangladeshi children with iron deficiency anemia (45), impressive benefits have been claimed in some case-reports (46, 47). These conflicting findings may be explained by genetic polymorphism of the organism, which may render some strains more prone to metabolize iron (48)

The mechanism by which *H. pylori* may lead to vitamin B12 deficiency, imply the presence of corpus atrophich gastritis (which is not the most frequent event related to *H. pylori* infection), and consequent low secretion of intrinsic factor necessary for cobalamin absorption. Once again, the organism may have clinical relevance in extreme clinical situations, such as hemodialysis patients (49); on the other hand, Van Oijen et al. failed to detect a contribution of the organism in other vitamin B12 associated states, such as alcoholism (50). Two studies recently reported an association of Chronic NSAIDS use and urticaria with cobalamin deficiency: both studies did not detect a role of *H. pylori* in determining this situation (51,52). A case report claimed persistent remission of megaloblastic anemia after *H. pylori* eradication (53).

Immunologic and allergic disorders

An immuno-mediated mechanism has been considered in many potentially *H. pylori* related disorders such as cardiovascular disease and idiopathic thrombocytopenic purpura. On this basis, studies have been performed on a possible role of the organism in classic immunologic and allergic disorders.

Two studies, evaluating opposite hypotheses, have been tested on a general role of *H. pylori* in allergy: the first one, based on the well known negative association between the presence of oro-fecally transmitted organisms and allergy, searched for a protective role of the organism in allergic

diathesis; the second one, based on the capability of *H. pylori* to increase gastric permeability, examined the possible predisposition to food allergy in infected subjects. Both studies (54,55) gave negative findings.

As far as the association with specific disorders is concerned, no association has been found in case-control studies concerning primary biliary cirrhosis (56), and rosacea (57). For the latter, the possibility of an association with specific histologic subtypes has been suggested (58).

A report based on response to eradication therapy (59) has suggested an association of *H. pylori* infection with thyroid autoantibodies, whereas a cross-sectional survey, including consecutive dyspeptic patients undergoing upper GI endoscopy, did not detect an increase in the prevalence of these autoantibodies (60). However, infection may be involved in specific autoimmune disorders such as Hashimoto thyroiditis (61), as suggested by Franceschi et al.

In a cross-sectional survey, Rybar et al. (62) observed that, among patients with rheumatoid arthritis, those with both IgG and IgA antibodies against *H. pylori* had a higher propensity to have involvement of sites other than joints. Altered intestinal permeability, induced by the organism, may explain the association with this disorder, as well as with other rheumatologic conditions, such as seronegative spondyloarthritis (63), and Sjogren's syndrome (64).

The mechanism underlying the possible association of urticaria with *H. pylori* remains still elusive. In fact, impressive benefit after eradication therapy has been reported (65,66). Furthermore, in one of the two above reported studies, no remission was observed in patients in whom antibiotic therapy failed to eradicate the organism (66). On the other hand, the same study did not show any difference in the rate of infection between patients and controls, and the proposed mechanism of *H. pylori* linked altered gastrointestinal permeability has not been demonstrated in infected patients with food related urticaria (67). It is possible that a IgA- and IgE-mediated immune response against antioxidative bacterial proteins may arise in some infected subjects, inducing this skin disorder (68).

One case-control study in patients with nasal polyps did not detect differences in the prevalence of

infection between patients and controls (69); the organism was however identified by immunohistochemistry in 6 specimens taken from polyps.

Miscellaneous

Among neurological disorders, Malaguarnera et al found significantly higher IgG levels against *H. pylori* in patients with Alzheimer disease than in controls (70). Similar findings have been reported in a case control study of patients with Guillain-Barrè syndrome (71): it is ironic that the controls of this study were represented by patients with iron deficiency anemia, a condition which might be related to *H. pylori* infection. A relationship with migraine has been suggested by Tunca et al (72), showing that the eradication of the bacterium can reduce frequency, duration and severity of clinical attacks of the disease. Finally, an impaired autonomic nervous function has been shown in infected patients with atypical chest pain by Budzynski et al (73)

Some interest has recently been generated on possible consequences of infection on body mass index.. Indeed infection may decrease serum ghrelin and increase gastric leptin levels, which may, in turn, decrease body mass index. On this basis, some studies have focused on these possible hormonal changes, whereas other reports pointed out to the clinical counterpart of these alterations. Ioannou et al.(74) measured serum leptin levels and body mass index in 6724 adult subjects: he was unable to find any relationship of these variables with the presence of infection. Similarly, Nishi et al. did not detect increased levels of serum leptin in infected patients, although they found an increased expression at the level of gastric mucosa (75) By contrast, relevant changes in gastric ghrelin expression (76), and in plasma ghrelin concentration (77) have been reported by Japanese authors after eradication therapy; furthermore, an increase of body mass index (78) has been reported in peptic ulcer patients one year after. It is possible that these non uniform findings may reflect the fact that substantial alterations in the levels of ghrelin may be observed only when infection induces gastric atrophy (79).

A possible causative role of *H. pylori* in upper respiratory infections and otitis media has been tested by Pitkaranta et al (80): they failed, however, to detect the organism from culture of samples of adenoid tissue and middle ear fluid. In the context of respiratory pathology, an increased sero-prevalence of *H. pylori* infection and especially of CagA positive strains, has been reported in a case-control study concerning 126 patients with chronic obstructive pulmonary disease (COPD), and 126 controls (81): a possible confounding role of concomitant cardiovascular disease cannot however be excluded. In another case-control study, no difference in the prevalence of infection was found between COPD patients and controls (82).

Response to eradication therapy has been examined in type 1 diabetes by Candelli et al. (83): they found a similar rate of eradication in subjects with the disease and in dyspeptic controls; furthermore, no improvement in glycemic control was observed in treated patients. An inverse association between infection and end stage renal failure has been reported in type 2 diabetic patients with renal insufficiency (84). However, this somewhat surprising finding was based on a small number of patients and should be confirmed by further larger series.

Hormonal changes, consisting in increased levels of circulating insulin like growth factor and cortisol have been reported (85); pathophysiologic premises for these alterations remain unclear, however.

As far as oral diseases are concerned, the possible involvement of *H. pylori* in teeth loss has ben tested by Peerce et al (86), who found a relationship between teeth loss and infection examining 334 individuals aging 50 years. The correlation was no longer detectable after multivariate analysis taking into account socio-economic status. A beneficial effect of eradication therapy in recurrent aphthous stomatitis has also been reported (87)

A possible correlation with ocular disorders has also been assessed: an increased prevalence of *H. pylori* infection in patients with central serous chorioretinopathy and diffuse retinal epitheliopathy, as compared with historical controls has been reported (88), whereas no relationship between infection and age related neovascular macular degeneration was found (89).

As far as the correlation with neoplasia is concerned, Nurgalieva et al (90), in an elegant case-control study, suggested a possible marginal role of H. pylori infection in laryngeal cancers not associated with HPV-16 infection; in another study, search for the organism by himmunohistochenical methods in normal and neoplastic laryngeal tissue yelded negative findings (91). Finally, on the basis of the findings of a case-control study, Philipou et al (92) denied a possible involvement of the organism in lung cancer.

An experimental study in mouse has shown an adverse outcome of pregnancy (higher numbers of resorption and lower fetal weights) in infected animals (93).These findings need to be confirmed in humans for assessing their clinical relevance.

There is some suggestion, based on detection of bacterial DNA (94), that *H. pylori* may be present in gallbladders harbouring cholesterol gallstones. It remains unclear, however, whether this organism is an innocent bystander or active participant in gallstone formation.

In hepatology, *Helicobacter* 16S rDNA (from *H. pylori*- and *H. pullorum*-like organisms) was found in only 4.2% of liver samples from controls and in 3.5% from patients with non-cirrothic chronic hepatitis C with respect to 68% of liver samples from patients with HCV positive cirrhosis without hepatocellular carcinoma and 61.3% from from patients with HCV positive cirrhosis with hepatocellular carcinoma (95). Another recent study found *Helicobacter* 16S rDNA to be present in 8 of 20 samples of primary liver carcinoma (6 showing high similarity to DNA of *H. pylori*) with respect to none in the control group (96). Results from these retrospective studies warrants prospective trials to determine the possible causal role of these bacteria in the progression of chronic hepatitis C and in hepatocarcinogenesis.

The suggestion that ammonia production due to bacterial urea breakdown may contribute to hepatic encephalopathy in patients with liver failure comes from a study showing an association between infection and the degree of porto-systemic encephalopathy (97).

OTHER *HELICOBACTERS*

Identification and classification

Human, primate and pig isolates of the large tightly coiled bacterium *'Helicobacter heilmannii'* have been characterized by phylogenetic analysis (98). Fifteen isolates clustered with *'Candidatus* Helicobacter suis', whereas 11 strains could not be differentiated from *Helicobacter bizzozeronii*, *Helicobacter felis* and *Helicobacter salomonis*. Urease gene analysis separated these isolates into the above three and a fourth distinct cluster containing human and feline isolates. This cluster of isolates was proposed as a unique species with the provisional name *'Candidatus* Helicobacter heilmannii' (98).

Helicobacter mastomyrinus was isolated from the liver and cecum of mastomys and from cecum and feces of normal mice (99). Based on 16S rDNA and phenotypic traits, the bacterium was closely related to *'Helicobacter muricola'* and expressed urease, cytolethal distending toxin and caused cell distention. Livers of mastomys from which this novel helicobacter was isolated showed mild inflammation around bile ducts and focal hepatitis with necrosis (99).

16S rDNA analysis may not differentiate helicobacters to the species level and does not necessarily correspond to results of polyphasic taxonomy. Gene analysis of the 60 kDa heat-shock protein (HSP60) demonstrated a higher resolution than conventional 16S rDNA for species identification of gastric and enterohepatic *Helicobacter* spp. (98, 100).

Characterization of 16S rRNA, ureaseB, and HSP60 gene sequences, DNA-DNA hybridization, as well as phenotypic analysis of Finnish canine and feline isolates as well as reference strains of *Helicobacter* sp. flexispira taxa 2, 3 and 8, demonstrated that these strains are members of the species *Helicobacter bilis* (101).

Diagnosis

A duplex PCR for routine analysis of *Helicobacter* species in murine feces utilized intestinal *Lactobacillus* species as an internal standard, demonstrating the usefulness of a quality control, extendable to other feces tests, to rule out false negative PCR results (102).

Novel gene targets for five common murine helicobacters, *H. bilis*, *Helicobacter hepaticus*, *Helicobacter muridarum*, *Helicobacter rodentium*, and *Helicobacter typhlonius*, have been used to construct a multiplex PCR-assay, allowing species-level detection of some common rodent species without subsequent restriction fragment analysis (RFLP) or DNA-sequencing (103). A recombinant immunoreactive protein (P167) of *H. bilis*, coupled to microbeads in a multiplex assay format, demonstrated sensitive and specific serodetection of *H. bilis* with high-throughput and low batch-to-batch variation (104).

Visualization of *Helicobacter* spp. using 16S rDNA probes, for *Helicobacteraceae* or specifically for *H. hepaticus* or *Helicobacter ganmani*, and fluorescent in situ hybridization (FISH), demonstrated spatial differences in helicobacter colonization of the mouse cecum (105).

Pathogenesis

Few candidate virulence factors of non-pylori *Helicobacter* spp. have been identified; however, the *H. hepaticus* cytolethal distending toxin (CDT), also expressed by some other enterohepatic *Helicobacter* species (EHS), was shown to mediate a previously described cytopathic effect on cultured cells. Isogenic *H. hepaticus* CDT-negative mutants colonized mice but with a markedly attenuated capacity to induce lesions in a murine IBD model (106).

Analysis of the lipopolysaccharide (LPS) of gastric and enterohepatic *Helicobacter* species demonstrated some structural heterogeneity in LPS-moieties and that LPSs of some EHS induced significantly lower *Limulus* amoebocyte lysate activity compared with *Helicobacter pylori*, nonetheless, the LPS of all analyzed species induced NF-κB activation in cultured cells (107).

Moreover, helicobacter LPS induced cytokine signaling mediated by Toll-like receptor (TLR) 4, whereas the cytokine response to intact gastric (*H. pylori*, *H. felis*) or EHS (*H. hepaticus*) was

mediated by TLR2, features that were observed using macrophages and monocytes as well as in mice with various TLR-deficiencies (108).

Animal models and natural infection

H. felis causes a persistent chronic inflammation that with time progresses to gastric cancer in some strains of mice, an established model of *H. pylori*-induced gastric disease in humans. Transgenic mice overexpressing amidated as well as glycine-extended gastrin were inoculated with *H. felis* and long-term effects included increased susceptibility to ulcer disease whereas *H. felis*-mediated preneoplastic progression was delayed (109).

In *H. felis* infected C57-mice oxyntic atrophy of the fundus is associated with a spasmolytic polypeptide expressing metaplastic (SPEM) cell lineage. Novel studies in this animal model described SPEM-related gene transcripts associated with gastritis cystica profunda and suggested that SPEM represents a precursor lineage of dysplasia in this animal model of gastric carcinogenesis (110).

BALB/c-mice do not develop clinical disease with either of the organisms *H. felis* or *Toxoplasma gondii*. However, long-term coinfection induced severe disease, including gastric atrophy and metaplastic changes, and increased mortality rates by modulating the host immune response towards a Th1 dominated phenotype (111).

'H. heilmannii' is prevalent in many animal species and causes gastric disease in a small percentage of patients. Specific pathogen-free mice inoculated with human and animal isolates of *'H. heilmannii'* developed gastric mucosa associated lymphoid tissue (MALT) lymphoma. More severe pathology was observed in animals infected with *'H. heilmannii'* as opposed to *H. felis* or *H. pylori* (112).

H. hepaticus induces chronic hepatitis that progresses to hepatocellular carcinoma in the A/JCr mouse. Studies of the pathogenesis of premalignant disease in this model revealed that early infection (first weeks of life) leads to disease development and that male mice are more susceptible

to infection (113). In this model of infectious liver cancer, hepatic gene expression profiles, monitored during one year of *H. hepaticus* infection, identified putative tumor markers that correlated with advancing hepatocellular dysplasia (114).

The influence of some EHS on cholesterol gallstone formation in susceptible C57L/J mice showed that cholesterol cholelithogenesis significantly accelerated in mice infected with *H. bilis* or dual-infected with *H. hepaticus* and *Helicobacter rodentium* (115).

H. rodentium has not been implicated in cecal or hepatic lesion formation in SCID or A/JCr mice, however, immunodeficient mice co-infected with *H. hepaticus* and *H. rodentium* displayed augmented disease compared with *H. hepaticus* infection alone (116).

Male A/JCr mice seem more susceptible to develop helicobacter-induced hepatic disease. However, in the same strain of mice chronically infected with *H. hepaticus*, female mice developed more severe intestinal inflammation than did infected male mice (117).

Murine-derived probiotic lactobacilli have been shown to reduce *H. hepaticus*-induced colitis in interleukin (IL) 10 deficient mice by modulation of the mucosal (TNF-α and IL-12) inflammatory response (118).

H. bilis caused mild to severe chronic inflammation of the liver of outbred Swiss mice and seroconversion to *H. bilis* outer membrane antigens was common in 6- to 8-month-old mice with hepatitis (119).

A systematic investigation of laboratory rodents demonstrated a high prevalence of *Helicobacter* species in several academic animal facilities. An endemic colonization pattern was observed and up to five *Helicobacter* species, identified by PCR denaturing gradient electrophoresis and sequencing were found in a single facility (120).

Chinese wild rodents, such as gerbils, jerboas and rats, are hosts for the common rodent species *H. hepaticus* and *H. ganmani*, as well as *Helicobacter winghamensis* and *Helicobacter canadensis* (121). The latter two species have been isolated from diarrheic humans.

Seven of 23 examined captive rabbits were positive for spiral gastric bacteria related to *H. felis*, *H. salomonis*, and a putative novel species by 16S rDNA analysis (122).

A high prevalence (>90%) of *'Candidatus* Helicobacter suis' was detected in pig stomach mucosa and gastric inflammation was common (>60%) among positive animals (123).

Spiral gastric bacteria in the stomach of cheetahs were similar to *'Helicobacter heilmannii'* by morphology and 16S rDNA analysis. Helicobacter-infected captive cheetahs displayed gastritis whereas wild cheetahs did not. Host factors likely account for disease development in the captive animals (124).

Possibly novel *Helicobacter* and *Wolinella* spp., related to helicobacters previously isolated in seals, otters and dolphins, and to *Wolinella succinogenes*, respectively, have been identified in sea lions with gastritis and ulceration (125).

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