Helicobacter pylori and oesophageal disease

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Helicobacter pylori (*HP*) causes chronic gastritis with variable activity and topographic distribution. Well established consequences are peptic ulcer disease and gastric neoplasia. As duodenal ulcer is often associated with gastro-oesophageal reflux disease (GORD) and antral gastritis is a frequent finding in patients with reflux disease, *HP* infection may be a common cause of both conditions.

Epidemiological aspects

Currently, we have no clear data to show that patients with GORD are more frequently infected by *HP* than controls. Indeed, some studies showed a significantly lower incidence of *HP* infection in patients with reflux disease than in matched controls. The prevalence of *HP* infection is decreasing steadily in white adults in developed countries. This is paralleled by an increasing incidence of GORD and its complications (e.g. adenocarcinoma of the oesophagus and the oesophago-gastric junction, respectively). Moreover, GORD and its consequences is uncommon in populations with a high prevalence of *HP* infection. The epidemiological data do not primarily support a role for *HP* in GORD, they rather suggest a protective role of the infection.

Clinical observations

Clinical trials looking at reflux symptoms following the cure of *HP* infection showed conflicting results. While some studies reported improvement of reflux symptoms, others did not, or indicated worsening of reflux symptoms. In this context, it has to be kept in mind that reflux symptoms are neither sensitive nor specific for GORD.

It has been reported that reflux oesophagitis may develop in healthy subjects and in patients with duodenal ulcer after successful treatment of *HP* infection. As GORD is a common disorder, this finding in small scale studies may be coincidental. However, in a large, controlled study we found that about one quarter of patients with duodenal ulcer cured of their *HP* infection developed endoscopically diagnosed reflux oesophagitis within three years of cure. This was double the rate we observed in patients with duodenal ulcer and ongoing infection. Multiple logistic regression analysis disclosed the severity of corpus gastritis before the cure, weight gain during follow-up and male gender as independent risk factors for post-eradication reflux oesophagitis.

Role of virulence factors (cagA)

A recent case-control study showed a lower prevalence of *HP* infection in patients with GORD of differing severity as compared to a carefully selected control group. In this study *HP* positive GORD patients were less frequently infected with cagA positive strains than were controls, and the incidence of cagA positive strains decreased with increasing severity of GORD and its complications. These data suggest a protective role of more virulent strains of *HP*.

Mechanisms by which *H. pylori* might protect against GORD

Several possible mechanisms by which *HP* could protect from reflux oesophagitis come to mind. *HP* may lower intragastric acidity. The amount of acid secreted in the infected stomach largely depends on the severity of corpus gastritis. More severe corpus gastritis is associated with lower acid output that returns to normal when the infection has been cured. This effect is probably mediated by cytokines and a loss of M3 receptors. Bicarbonate leakage from the inflamed mucosa and intramural back-diffusion of hydrogen ions may also lower the acidity in the infected stomach. *HP* gastritis may progress to multifocal atrophic gastritis with destruction of gastric glands and, in turn, hypochlorhydria. *HP* generates large amounts of ammonia, being a powerful neutralising substance. Ammonia could,

therefore, decrease the corrosive potential of the gastric juice refluxing into the oesophagus. Ammonia may also lead to protective adaptation of the oesophageal mucosa. Finally, it has been shown repeatedly that *HP* infection is associated with raised serum gastrin concentrations that decrease after cure of the infection. Gastrin, even at physiological concentrations, increase the pressure of the lower oesophageal sphincter.

Impact of *H. pylori* on the efficacy of antisecretory drugs

Proton pump inhibitors (PPIs) are without doubt the most effective drugs in the control of GORD. Pharmacological studies have clearly shown that *HP* renders PPIs more effective with respect to acid control, both in healthy subjects and in patients with duodenal ulcer. The clinical relevance of this finding has been proven recently, as maintenance therapy with omperazole was more effective in patients with GORD and associated *HP* infection than in uninfected GORD patients.

Impact of antisecretory drugs on *H. pylori* gastritis

Several studies have shown that treatment with an antisecretory drug is associated with worsening of corpus gastritis in *HP* infected patients. A controlled study by Kuipers and co-workers suggested that PPI maintenance treatment in *HP* positive patients with GORD may accelerate the development of atrophic corpus gastritis. However, this study is scientifically flawed by incorporation of an inappropriate control group. A randomized, controlled study available in abstract form only did not show a higher incidence of atrophic gastritis in *HP* positive patients on omeprazole as compared to *HP* positive patients receiving anti reflux surgery.

Conclusions

The inter-relation between *HP* and GORD is complex and not fully understood. There is no clear indication that *HP* could cause GORD, there is, however, some evidence to suggest that *HP* may protect from reflux oesophagitis. On the basis of the currently available literature it may be hypothesized that certain subjects with high gastric acid secretion are at risk for development of reflux oesophagitis: however, when these subjects are infected with a cagA positive *HP* strain, duodenal ulcer instead develops. Curing the infection in GORD may have the disadvantage of reducing the efficacy of antisecretory treatment; conversely, it may prevent worsening of corpus gastritis.