Helicobacter pylori and vascular diseases: Evidence and controversy

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Background

Classical risk factors for atherosclerosis, including behaviors or habits at which may be predictive future acute or chronic coronary artery disease, do not coincide with the global epidemiological pattern of atherosclerotic vascular diseases. There should be some other unknown mechanism underlying the pathogenesis of atherosclerosis.

Based on the discrepancy between coronary risk factors distribution and prevalence of ischaemic heart disease (IHD), some authors hypotesized that infectious agents, such as Chlamydia or Herpes viruses, may promote atherogenesis by affecting endothelial cells.[1,2] To support this observation, in the last few years emerging evidences proved that a chronic inflammatory status is associated with an increased risk of vascular disease and that immunological events are clearly involved in the atherosclerotic process.[3,4]

The well known pathological models of "acute infection-illness" is in contrast with the underhand and long term effect on immune system exerted by chronic infections. Such effect includes the release of cytokines and eicosanoids, which are endowed with a proinflammatory and vasoactive action. This phenomenon may promote atherosclerotic injuries. Moreover, many conditions related with vascular pathology, such as hypercoagulability, presence of circulating immune complexes and oxidative metabolites, high triglyceride levels, and autoantibodies against *Heat shock proteins*, have been hypothesized to be due to some chronic infectious agents.

Helicobacter pylori **and ischemic heart disease**

Helicobacter pylori (*H. pylori*) is one of the most frequent gastrointestinal infections worldwide. It is known that the immunological response elicited by this bacterium is an important determinant of the gastric mucosal damage.[5] In particular, the production of large amounts of various proinflammatory substances, such as cytokines, eicosanoids and proteins of the acute phase follows the gastric colonization.[5] Upon the basis of these observations, much interest has grown about its role in most extraintestinal disorders, among which, vascular diseases.

H. pylori infection, in particular, may induce a persistent increased production of interleukin (IL)-6,[6] which possesses pro-inflammatory and procoagulative properties. Interestingly, IL-6 is also able to increase C reactive protein plasma levels which represent a well known potential risk factor for future myocardial ischaemic events.[7-10] Il-1 and Tumor necrosis factor alfa (TNFα), which are, in turn, highly likely to be produced after the infection; may activate the endothelium causing various degrees of dysfunction. It also as been postulated an autoimmune mechanism based on the expression by *H. pylori* of a protein similar to human Heat Shock Protein 60 (HSP 60) commonly detectable at the site of plaque.[10]

Only a few prospective studies have been carried out, and all of them show poorer results than cross-sectional studies. Aromaa et al.[11], after studying a number of 3471 male patients among a period of 12 years did not reject the idea of a possible correlation, even if not statistically significant. Another study, with negative results was carried out over a population of 21.520 subjects, but its socioeconomic standard was too high to adequately represent the general population.[12]

It is known that some *H. pylori* strains with particular regard to those endowed with a pathogenicity islet able to produce a cytotoxin named cytotoxin associated gene- A (Cag-A) show higher virulence properties. Several studies, in particular, showed that these strains may evoke an increased inflammatory response with release of IL-8 and other proinflammatory substances directly by

gastric epithelial cells.[12,13] Aimed to elucidate on the role of *H. pylori* in IHD some researchers recently found increased prevalence of CagA-positive *H. pylori* strains among patients affected by IHD.[14] They concluded that this finding may better explain the pathogenic mechanisms of such association.

Finally, an extensive study showed that there is no difference in *H. pylori* positivity between patients presenting an acute (myocardial infarction, unstable angina) or a chronic clinical syndrome (chronic stable angina) of IHD.[15]

However, the majority of studies on correlation between *H. pylori* and vascular diseases are seroepidemiological and based on a retrospective analysis of immunological status of patients and controls. These studies contribute to create a scenery which is, for some aspects, rather confused. In particular, positive results for a correlation[16-18] are counterpointed by strikingly negative findings.[19] To explain these different results it has to be considered that potential confounding factors, such as low socioeconomical status, geographical provenience or gender, appear to be strongly associated both with *H. pylori* infection and coronary heart disease. To solve the problem, a recent metanalysis by Danesh et al on the studies carried out on the association between *H. pylori* and IHD, clearly showed that when controls were opportunistically recruited and not adjusted for confounding factors, a strong association was reported, conversely, the majority of studies which took into account of confounders reported a weak association.[12,13] On the other hand, it has to be remarked that some investigators failed to use the same diagnostic criteria for patients recruitment, in some cases assessing disease status with questionnaires rather than documenting presence of atherosclerotic plaques using angiography. Thus, further prospective studies remain to be performed, together with an accurate selection of patients and clinical documentation of their syndromes, joint with an age-sex matching of controls as precise as possible.

H. pylori and other vascular diseases

A recent attempt to determine a possible role for *H. pylori* in ischaemic cerebrovascular disease was performed using Doppler ultrasound scan to characterize the carotid atheromas. Results showed that *H. pylori* is strictly associated both with large vessel disease and lacunar stroke, but not to stroke due to cardioembolism or to unknown aetiology. Moreover, carotid stenoses of more relevant size were reported in association with *H. pylori* seropositivity. Finally, no difference was found between *H. pylori* infection status and the clinical onset of cerebrovascular disease. In fact, the seroprevalence between patients with stroke and transient ischaemic attack resulted the same.[20]

Since the release of large amounts of vasoactive substances, such as cy-

tokines and eicosanoids, follows the gastric colonization by *H. pylori*, some authors also investigated the possible role of the bacterium in some functional vascular disorders. Results showed that *H. pylori* infection is very common in two typical functional vascular disorders such as primary Raynaud's phenomenon and idiopathic Migraine. Moreover, a significant amelioration of the manifestations of both the diseases has been observed after *H. pylori* eradication.[21,22] Controlled eradication studies, however, still need to be performed and the exact sequence of events that could link *H. pylori* infection to functional vascular disorders remains to be identified.

Summary

An association between *H. pylori* and some cardiovascular diseases has been reported. At present, however, remains to be determined whether most of the associations found were casual or causal, given the huge amount potential confounding factors. In particular, further difficulty in the analysis of data is represented by the heterogeneity of the cases recruitment methods; in fact, some observations are based on cross-sectional studies, some on case-control studies while some other on simple case reports. Moreover, various diagnostic methods were used to assess cardiovascular diseases in different studies ranging from simple clinical history and ECG to coronary angiography. Only few studies included full evaluation of risk factors for atherosclerosis, such as cholesterol and fibrinogen status, arterial hypertension cigarette smoking or diabetes mellitus. Furthermore, as to concern detection of infectious agents, the majority of studies are seroepidemiological and involve antibody measurements, while at present there are not reports of the evidence of *H. pylori* or of its genome sequences in atheromatous and non-atheromatous blood vessels.

Residual confounding factors could also explain the weak epidemiological association reported by Authors. However, it should be pointed out that the recent report by Pasceri et al showing an increase in Cag-A-positive *H. pylori* strains in patients with IHD can be more effective for a correlation because the seroprevalence for a particular strain is *per se* independent of socioeconomic status or other confounders.

In conclusion, further studies based both on the molecular mechanisms of infection-triggered vascular damage and on *H. pylori* eradication protocols in cardiovascular patients remain needed to clarify if this supposed association is really fact or fancy.

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