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Editorial

Helicobacter pylori and ischemic heart

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Classical risk factors for atherosclerosis fail to completely explain the incidence of cardiovascular disease. Increasing evidences, dating from nineteen century observations to current studies, have shown that atherosclerosis is mostly an inflammatory disease and that coronary heart disease status and prognosis have strong relationships with inflammation[1,2].

On their way to find possible triggers for chronic inflammation, many authors noticed that various types of chronic infection, as those given by *Helicobacter pylori* and Chlamydia pneumoniae, are associated with an increase in risk factors and prognostic markers of ischemic heart disease (IHD). These chronic persistent infections in a variable number of cases run a symptomless course in infected subjects. Also for this reason, the impact of such a chronic infection on the immune system is hidden and long-term. In particular, the role hypothesized for *Helicobacter pylori* in the pathogenesis of cardiovascular diseases oversteps the well known pathological models of "acute infection-illness" and could bring new insights for the comprehension of conditions previously labelled as "idiopathic" or "functional".

Helicobacter pylori (*H. pylori*) is one of the most frequent gastrointestinal infections worldwide. The immunological response this bacterium elicits is a mainstay determinant of gastric mucosal damage. 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[3]. Upon the basis of these observations, much interest has grown about its role in most extraintestinal disorders, among which, cardiovascular diseases.

Interest of many authors has been to isolate laboratory values associated with a high risk of the onset or worsening of clinical coronary artery disease. Afterwards, a possible link of these values with chronic infection carrier status was sought. Many conditions related with vascular pathology, such as hypercoagulability, presence of circulating immune complexes and oxidative metabolites, an increase in leukocytes blood count, altered serum lipid profile, resulted associated with *H. pylori*. This agent may also induce a persistent increased production of interleukin (IL)-6, which possesses proinflammatory and procoagulative properties. IL-6 is also able to increase C reactive protein plasma levels[4]. This acute phase reactant, widely popular in general practice as an aspecific diagnostic marker, represents a well known potential risk factor for future myocardial ischaemic events[5-8]. Il-1 and Tumor necrosis factor alfa (TNFa) are, in turn, higly likely to be produced after H.pylori infection. Their action on the endothelium causes various degrees of disfunction. It also has 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 8.

First clinico-epidemiological evidences for a correlation between *H. pylori* and ischemic heart disease came out in a 1994 retrospective study. Since then, many authors reported a correlation time to time strong or spurious. However, data resulted often confused because of a lack of adjustment for other car-

diovascular risk factors. Conclusions from these studies cannot be univocally drawn, but correlation cannot be excluded[10].

Only few prospective studies have been carried out. Actually, *H. pylori* relevance in the pathogenesis of peptic ulcer disease emerged relatively recently, and atherosclerotic lesions tend to develop gradually in the time. Therefore, prospective long-term studies risk to be a bluff, since *H. pylori* seropositivity is often determined on the basis of a retrospective analysis on serum samples stored years before, and the sense of the investigation may be lost. However, Aromaa et al studied 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[11]. 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].

A new emerging field of interest is the multeplicity of *H. pylori* strains each having a different grade of pathogenicity. In particular, it is known that *H. pylori* strains endowed with a pathogenicity islet able to produce a cytotoxin named cytotoxin associated gene-A (Cag-A), show higher virulence properties. Cag-A strains, in fact, may evoke an increased inflammatory response with release of IL-8 and other proinflammatory substances directly by gastric epithelial cells. Aimed to shed light 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[13]. They also found no difference in *H. pylori* positivity between patients presenting with an acute (myocardial infarction, unstable angina) or with a chronic clinical syndrome (chronic stable angina) of IHD. This findings may help to explain the pathogenic mechanisms of such association. These data make it also clear that CagA status should be investigated rather than mere anti *H. pylori* antibodies in coronary patients. In fact, anti *H. pylori* positivity could itself represent a confounding factor. Moreover, the seroprevalence for a particular strain is per se independent of socioeconomic status or other confounders.

In conclusion, at present remains not clear if most of the associations found were casual or causal, given the huge amount potential confounding factors. Patients' recruitment methods are heterogeneous, and most of the observations are based on cross-sectional studies, many on case-control studies, some other on simple case reports. Moreover, unomogeneous diagnostic methods were used to assess cardiovascular diseases among studies ranging from simple clinical history and ECG to coronary angiography and full evaluation of the risk factors for atherosclerosis, such as cholesterol and fibrinogen status, high blood pressure, diabetes mellitus, smoke, have not always been performed.

Future studies should be focused on the molecular mechanisms by which peculiar virulent *H. pylori* may determine vascular damage and on the key role of the individual host immune response to the infection, which, at present, seems to be crucial for the development of extraintestinal diseases after the infection.

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