

Current view

Extragastric manifestations of *Helicobacter pylori* infection: a critical reappraisal

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SUMMARY

In recent years numerous studies have advocated a role for *Helicobacter pylori* in causing a variety of extragastric manifestations. These situations include Hematologic disorders such as iron-deficiency anemia and idiopathic thrombocytopenic purpura, vascular disorders such as ischemic heart disease, cerebral stroke, primary Raynaud phenomenon and primary headache, autoimmune diseases such as Sjogren's syndrome, Henoch-Schonlein purpura, autoimmune thyroiditis, idiopathic arrhythmias, Parkinson's disease, nonarterial anterior optic ischemic neuropathy, cutaneous disorders, such as rosacea, pediatric diseases such as growth retardation and sudden infant death syndrome, renal failure, diabetes mellitus, respiratory disorders, and glaucoma. However, many of these reports suffer for being either case reports or case series without suitable controls. More importantly many of these reports include inadequate numbers of patients. Therefore, it could be supported that purported manifestations may represent a coincidental phenomenon. However, there are some situations that could really represent a true extragastric manifestation. These situations include sideropenic anemia (refractory iron deficiency) and immune thrombocytopenic purpura due to molecular mimicry. The search in this field must be continued using large number of patients and suitable controls. Confirmation of these results could probably modify our therapeutic guidelines for some disorders.

Key words: *Helicobacter pylori*, Extragastric manifestations, Infections

1. INTRODUCTION

In recent years, in many extradigestive diseases, a putative pathogenetic role has been ascribed to *Hp* infection. Increasing evidence supports *Hp* infection as a cause of iron-deficiency anemia, while moderate evidence supports *Hp* infection as a cause of some cases of idiopathic thrombocytopenic purpura due to molecular mimicry.¹⁻⁴ It has been proposed that activation of inflammatory mediators by *Hp* seems to be the pathogenetic mechanism underlying the association between *Hp* infection and extragastric manifestations.

It must be stressed however, that most of the available data are conflicting because of the presence of many confounding factors in the published epidemiological studies. Moreover, many of the published reports suffer for being case reports or case-series without an adequate number of controls. Therefore, one can assume that the reported manifestations could simply be coincidental in nature.

The aim of this report is to answer the following question: Which of the reported associations are really related to *Hp* infection? We will try to answer this question by critically analyzing the available data of the international literature.

2. EXTRADIGESTIVE MANIFESTATIONS AND *HP* INFECTION

The reported associations of *Hp* infection with extragastric disorders are shown in table 1 and analyzed subsequently.

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Hematologic disorders

Iron-deficiency anemia

Epidemiological studies suggest that *Hp* infection is associated with iron deficiency as well as iron-deficiency anemia, regardless of the presence or absence of peptic ulcer disease. In the USA a recent report claims that *Hp* infection is associated with decreased serum ferritin levels and with a 40% increase in the prevalence of iron deficiency.⁵

It has been described that in subjects with *Hp* positive gastritis, concomitant changes in intragastric pH and ascorbic acid are present and might play a role in impairing alimentary iron absorption with consequent sideropenic anemia. It has also been speculated that *Hp* infected antrum could act as a sequestering focus for iron. *Hp* enhances gastric lactoferrin which captures iron from transferring. The iron thus bound to lactoferrin which is picked up by the bacterium by means of its outer membrane receptors is used for its own growth⁶. These models, however, are not able to answer the question of why iron-deficiency anemia does not develop in all infected subjects.

Recent data also support a relationship between iron deficient anemia and *Hp* infection in areas with high rates of *Hp* infection. In rural Alaska, a region in which natives have a high prevalence of iron deficiency and *Hp* infection, active *Hp* infection was independently associated with iron deficiency and iron-deficiency anemia among children.⁷

Polymorphism of *Hp* strains may be one of the factors determining the occurrence of *Hp*-associated iron deficiency anemia.⁸

Recently, a new anti-microbial liver-made peptide, namely hepcidin, has been characterized. The link between hepcidin induction, inflammation and anemia both in humans and in animal models supports its key role as mediator of anemia of inflammation.

Vitamin B12 deficiency

It has previously been suggested that *Hp* infection could be related to impaired cobalamin absorption and consequently elevated homocysteine levels, thus explaining why *Hp* infection is associated with coronary heart disease. So far, several studies have been published related to *Hp* status and homocysteine, *Hp* infection and cobalamin status, or both. Critical analysis of these studies suggests that most of them differ in terms of definition of *Hp* status, measurement of cobalamin status, suit-

able selection of study cohorts and geographical areas. Therefore the results must be considered at the moment as inconclusive, not suggesting a major role for *Hp* infection in the development of cobalamin deficiency and elevation of plasma homocysteine levels.⁹ However, recent findings challenge the common notion that pernicious anemia is a disease of the elderly and imply a disease starting many years before the establishment of clinical cobalamin deficiency by an autoimmune process likely triggered by *Hp* infection.¹⁰ Moreover, *Hp* positive chronic hemodialysis may present with lower cobalamin blood levels and macrocytosis compared to *Hp* negative patients.¹¹

Idiopathic thrombocytopenic purpura

In 1998 Gasbarrini et al for first time reported a high prevalence of *Hp* infection in patients with idiopathic thrombocytopenic purpura (ITP) and showed that platelet recovery occurred after successful eradication of the microorganism in most of cases.¹² Since then, there have been increasing data regarding the association between *Hp* infection and ITP and a significant increase in platelet count after bacterial eradication.

Most of the studies reported so far described a positive association between *Hp* infection and ITP. Eradication of *Hp* resulted in a significant increase in the platelets count in more than 50% of positive *Hp* cases, suggesting that *Hp* infection is involved in the mechanisms of thrombocytopenia in a large number of middle-aged and older IPT patients.^{13,14}

Table 2 shows the results of some of the recently published studies.¹⁵⁻¹⁸ As indicated in the table, most of these studies reported complete or partial remission in more than 50% of cases, which lasted for at least one year. However, the number of cases varies significantly in some, while in others follow-up is lacking. In a recently published review,¹⁴ the number of cases included in all relevant studies is 1126, the number of infected persons 723. Bacterial eradication was achieved in 81% and the response (increase in the number of platelets) rate of 53% lasted from 4 to 31 months.

Many possible explanations concerning the beneficial role of *Hp* eradication have been proposed.¹⁴ Among them, the most important is that *Hp* infection could induce antibody production in response to antigens that cross-react against various platelet glycoprotein antigens. It has been proposed that cross-reacting autoantibodies against CagA may play a pathogenic role in at least some proportion of patients with ITP. Finally, genetic influ-

ences (difference in HLA class II allele patterns between ITP patients with or without *Hp* infection) may also be implied in the development of thrombocytopenia in *Hp* infection.

We can suggest that in order to confirm the effectiveness of eradication therapy in ITP positive cases, prospective studies using a large number of patients with a long follow-up, are required.

Respiratory disorders

Chronic bronchitis – Pulmonary tuberculosis

A small number of epidemiological and serologic case-control studies suggest that *Hp* infection may be associated with the development of chronic bronchitis.¹⁹ Similarly a frequent association between *Hp* infection and pulmonary tuberculosis has been found.²⁰

Bronchiectasis – Lung cancer

A small number of data suggest that patients with lung cancer or bronchiectasis exhibit an increased rate of *Hp* seroprevalence. However, *Hp* could not be detected in bronchial specimens derived from patients with bronchiectasis.²¹

Bronchial asthma

It was suggested that bronchial asthma seems not to be related to *Hp* infection. This assumption was confirmed in a recently published study.²²

Obstructive sleep apnoea

A positive association between *Hp* infection and obstructive sleep apnoea was reported in a small trial. However, these results were not so far confirmed.²³

All associations between respiratory diseases and *Hp* infection are based on case-control studies including small numbers of patients. It is of interest that there is no study focusing on the possible pathogenetic mechanism linking respiratory disorders and *Hp* infection. Therefore, prospective studies including large numbers of patients are needed in order to confirm the possible relationship between *Hp* infection and respiratory diseases.

Ischemic heart disease

Chronic infections have been demonstrated to be early factors of atherosclerosis and cardiovascular diseases. It has also been demonstrated that their relevance increases when they are caused by agents with a broad spectrum of virulence such is *Hp* infection. A large number of studies have been published concerning the

possible correlation between *Hp* infection and ischemic heart disease based on the proposed role of some chronic infections in the pathogenesis of vessel wall injury and atheromatous plaque.²⁴

It has been proposed that asymmetric dimethylarginine (an endogenous inhibitor of nitric oxide synthase) may increase in infections and plays an important role impairing the vascular functions of the endothelium. In a recently published study it was found that *Hp* infection increases asymmetric dimethylarginine levels.²⁵ Eradication of *Hp* could theoretically lead to a decrease in asymmetric dimethylarginine levels, thus reducing the risk for cardiovascular disease.

Epidemiological studies as well as eradicating trials have produced conflicting results. However, studies investigating the molecular mimicry mechanisms induced by *Hp* strongly support the association.

It must be stressed that none of the studies published so far have taken into account the effect of genetic susceptibility to develop ischemic heart disease or to respond to *Hp* infection. It must also be stressed that due to the fact that many patients develop ischemic heart disease in the absence of any risk factor, no condition or exposure completely explains the occurrence and progression of the disease.²⁶

Among the factors contributing to the development of atherosclerosis, atrophic gastritis seems to be involved in its pathogenesis via the development of hyperhomocysteinemia, which is an independent risk factor for ischemic heart disease.

A recent meta-analysis suggest that periodontal disease caused by a variety of microorganisms including *Hp*, may indeed contribute to the pathogenesis of cardiovascular disease at least by 20%, while the risk for stroke is even higher.²⁷ Infection by *Hp* could well be involved in the pathogenesis of ischemic heart disease by releasing cytokines and other pro-inflammatory mediators that may initiate a cascade of biochemical reactions causing endothelial damage and facilitate cholesterol plaque attachment.

Glaucoma

In 2002, Kountouras et al described that patients with glaucoma have an increased rate of *Hp* infection compared to the normal population.²⁸ They also found that successful eradication of *Hp* resulted in significant fall in the mean intraocular pressure and improvement in all visual field parameters examined. In a subsequent prospective case-control study from Canada, which includ-

ed large number of patients and matched normal controls, seropositivity for *Hp* was higher in the glaucoma group but did not reach statistical significance.²⁹ The authors conclude that *Hp* infection is not associated with open-angle glaucoma. There is no obvious explanation for this discrepancy. However, differences in the *Hp* infection rate between different countries could influence the observed results as the rate of positivity for *Hp* in glaucoma patients was 88% in the Greek study and 26% in the Canadian study. Further studies are needed in order to further clarify this interesting subject.

Skin

Rosacea

Rosacea is one of the most common conditions der-

Table 1. Extradigestive manifestations of *Helicobacter pylori* infection

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- Hematologic disorders
 - Iron-deficiency anemia
 - Idiopathic thrombocytopenic purpura
 - Vascular
 - Ischemic heart disease
 - Cerebral stroke
 - Primary Raynaud phenomenon
 - Primary headache
 - Autoimmune
 - Sjogren's syndrome
 - Henoch-Schonlein purpura
 - Autoimmune thyroiditis
 - Idiopathic arrhythmias
 - Parkinson's disease
 - Nonarterial anterior optic ischemic neuropathy
 - Cutaneous
 - Rosacea
 - Chronic idiopathic urticaria
 - Alopecia areata
 - Pediatric diseases
 - Growth retardation
 - Sudden infant death syndrome
 - Renal failure
 - Diabetes mellitus
 - Respiratory disorders
 - Glaucoma
 - Late menarche
 - Anorexia of aging
 - Hepatic encephalopathy
-

matologists face. The cause of this condition remains somewhat of a mystery. Several hypotheses have been documented. Among them *Hp* infection seems to be quite significant.³⁰

Eradication of *Hp* seems to be of value in patients with rosacea.^{31,32} It must be emphasized that the prevalence of *Hp* infection is not higher in patients with rosacea, compared with normal controls.³³

Diabetes mellitus

Recent studies suggest that diabetic patients exhibit a high prevalence of *Hp* infection and it is correlated with dyspeptic symptoms.³⁴ Diabetic patients complicated with autonomic neuropathy and dyspepsia, have a high rate of *Hp* infection and should be carefully investigated and considered for *Hp* eradication therapy. However results concerning the possible positive influence on the course of these complications after successful eradication of *Hp* are lacking.

Urinary tract

It has been proposed that high serum urea nitrogen seems to correlate with low prevalence of *Hp* infection. In a relevant study of 53 *Hp* positive patients with renal failure it was found (on multivariate analysis) that high serum urea nitrogen level was the only factor significantly associated with *Hp* infection.³⁵

In another study it was found that long-term dialysis decreases the prevalence of *Hp* infection.³⁶ In patients receiving dialysis the prevalence of *Hp* infection was 27.5% while in non-dialysis patients the prevalence of *Hp* infection was significantly higher (56%). It seems therefore, that hemodialysis patients with high serum urea nitrogen may be protected against *Hp* infection. The reduction of gastric acid secretion related to chronic gastritis may be involved.³⁷

Conclusion

The available results suggest that there are some situations that could represent a true extragastric manifestation of *Hp* infection. These situations include sideropenic anemia (refractory iron deficiency) and immune thrombocytopenic purpura due to molecular mimicry. In other situations the involvement of *Hp* infection in their pathogenesis seems to be weaker. Research in this field must be continued using a large number of patients and suitable controls. It seems possible that confirmation of these results could modify our therapeutic guidelines for some disorders.

Table 2. Idiopathic thrombocytopenic purpura and *Helicobacter pylori* infection

Author-year	No of pts	Hp(+) cases	Platelet increase after successful eradication	Platelet increase after unsuccessful eradication	Complete remission	Partial remission	Overall remission
Fujimura et al 2005	300	207	63%	33%	23% after 12 months	42% after 12 months	65% after 32 months
Veneri et al 2005	43	significant increase of PLTs after successful eradication					49% after 31 months (20 pts)
Suzuki et al 2005	36	25 (85% eradication)	46%	0%			NR
Tsutsumi et al 2005	9	9	4/9	2/9			NR

NR: not reported

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