Review article

# Association between Helicobacter pylori and open angle glaucoma: current perspective

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**Abstract**

*Helicobacter pylori* is a Gram negative, spiral-shaped, strictly micro-aerophilic and flagellate human pathogen that can inhabit many areas of stomach. *H. pylori* infection leads to the generation of oxygen free radicals. *H. pylori* infection might also aggravate the course of glaucoma by increasing the levels of nitric oxide, endothelin-1 and free radicals indirectly. This article briefly reviews the current perspectives on this issue.

**Keywords:** Helicobacter pylori, glaucoma, free radicals

## Introduction

### Helicobacter pylori infection, its prevalence and transmission

*Helicobacter pylori* is a Gram negative, spiral-shaped, strictly micro-aerophilic and flagellate human pathogen that can inhabit many areas of stomach. In 1983, Warren and Marshal established the role of *Helicobacter pylori* in the human gastric mucosa which later on was identified as a causative factor for gastritis and duodenal ulcers and as a risk factor for malignancies of the stomach (Marshall and Warren 1984; Misiewicz and Pounder, 1996). Recent evidence indicates that *H. pylori* infection is also associated with cardiovascular, immunological, and various other extradigestive pathologies (Gasbarrini *et al* 1999; Blei, 2001; Marrollo, 2001. In addition, *H. pylori* infection leads to the generation of oxygen free radicals (Everett *et al* 2001; Danese *et al* 2001) which are reported to be involved in ganglion cell death (Osborne *et al* 1999) while circulating cytokines is reported to increase following *H. pylori* infection (Fu *et al* 1999). Moreover, *H. pylori* infection might also aggravate the course of glaucoma by increasing the levels of nitric oxide, endothelin-1 and free radicals indirectly. However, in order to consider *H. pylori* as a risk factor for glaucoma, numerous histologically *H. pylori* positive patients should be searched for glaucoma.

The genus *Helicobacter* originally contained two species namely, *H. pylori* and *H. mustelae*. *Helicobacter pylori* differs from the genus *Campylobacter* (Gram-negative, spiral, microaerophilic, motile and oxidase-positive bacteria) in its unique specific fatty acid profile, ultra structure and morphology, respiratory quinines, growth requirements, enzyme capabilities and a distinct RNA sequence. Though, *Helicobacter pylori* invariably infect humans and monkey but have recently been reported to infect domestic and pet animals like, cats, as well. It is non invasive, living in the mucus that overlies gastric-type mucosae, to which a small proportion of the bacterial cells are attached and exhibit efficient urease activity which plays a pivotal role in colonization and may be important in the development and maintenance of infection. Urease, which does not occur normally in humans, cleaves urea to ammonia and CO2. In turn, ammonia increases the pH of the adjacent gastric fluids, stimulating the release of the peptide hormone gastrin which after reaching the systemic circulation produces vasodilatation. *H. pylori* infection results in elevated gastrin blood levels and the eradication of *H. pylori* reduces gastrin blood levels (Russo *et al* 2001). Gastrin may increase the levels of potent vasodilator nitric oxide. It was also shown that

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the expression of nitric oxide synthase is increased in *H. pylori* infection (Fu *et al* 1999; Antos *et al* 2001).

Megraud *et al* (1989) reported that in developing countries, the organism is acquired early in childhood and by the age of 10, 50%-60% children are infected while it affect up to 90% adults. The data collected by Gill *et al* (1993) indicated that in India exposure to *H. pylori* is widespread and occurs during early age accounting for about 83% of the populations. On the contrary, in developing countries most infections occur in childhood with prevalence rate exceeding as high as 50% at age 10 and 80% during adulthood (Graham *et al* 1988). In contrast, in developed countries, few infections occur during childhood and a gradual increase in prevalence with age (at a rate of about 0.5-1% per year) is observed leading to infection rates of 20-30% by the age of 20 and about 50% at 50-60 years. In developed countries, the sero-prevalence rates are however, invariably significant among different ethic groups suggesting that socioeconomic conditions, such as, crowding, poor sanitation and close contact with infected persons during childhood may be risk factors for its rapid spread among human populations.

Though humans are the natural hosts for *H. pylori,* the exact route and source of infection is unclear. However, person to person transmission is probably the prominent mode of its spread, although controversy exists over whether faeco-oral or oral-oral spread route predominates. In this context, Gill *et al* (1993) suggested a faeco-oral route of transmission after assessing the epidemiological data collected from both developed and developing nations. The marked differences in *H. pylori* infection, especially in the first few decades of life led to this conclusion. The main epidemiological evidence supporting faeco-oral transmission is similar to the sero-epidemiology of hepatitis A (Graham *et al* 1991), but *H. pylori* have been isolated from saliva (Ferguson et al., 1993), from dental plaques (Shames *et al* 1989) and also from the feces (Thomas *et al* 1992, Kelly *et al* 1994) by polymerase chain reaction (PCR) suggesting that transmission by both routes are responsible for its spread (Mapstone *et al* 1993).

**Pathogenesis of glaucomatous optic neuropathy**

Glaucoma is the second prominent cause of blindness in the world, afflicting about 67 million people. In the United States alone, over three million peoples are reported to suffer from this disease, and about 300,000 new cases are diagnosed annually (www.ahaf.org/glaucoma/about/glabout.htm). Of the various forms of glaucoma, the most prevalent form of this disease is *open-angle glaucoma,* where damage to the optic nerve may occur perniciously, without any significant vision damage in the early stages. Besides other factors causing glaucoma, the current issue is whether persons suffering from *H. pylori* infection can also have high risk of glaucoma than uninfected subjects even-though *Helicobacter pylori* remains one of the world's most prevalent bacterial pathogens, often causing gastritis, peptic ulcer disease, gastric mucosa-associated lymphatic tissue lymphoma, or gastric adenocarcinoma. Various theories have been proposed regarding the pathogenesis of glaucomatous optic neuropathy. In 1858, Muller proposed that the elevated intra-ocular pressure (IOP) caused a direct compression and heightened IOP led to the death of the neurons (the mechanical theory), while von Jaeger in the same year suggested that a vascular abnormality leads to optic atrophy (the vascular theory). In 1892, Schnabel reported that atrophy of neural elements created empty spaces, which pulled the nerve head posteriorly (Schnabel's Cavernous atrophy). In the early 20th century, the mechanical theory received more support and acceptance until La Grange and Beauvieux popularized the vascular theory in 1925. It was generally regarded that glaucomatous optic neuropathy was secondary to ischaemia. In 1968, the role of axoplasmic flow in glaucomatous optic neuropathy was introduced, reviving the support for the mechanical theory but not excluding the possible influence of ischaemia which plays a role in the obstruction of axoplasmic flow in response to elevated IOP.

Levin and Louhab (1996) in a clinico-pathologic report identified retinal ganglion cells undergoing apoptosis in one eye of a 70-year-old man with anterior ischaemic optic neuropathy. The probable explanation for their finding was that the eye underwent functional optic nerve axotomy. Current studies indicate that apoptosis is a mechanism of cell death in several important ocular and gastrointestinal diseases including glaucoma, retinitis pigmentosa, cataract formation, retinoblastoma, retinal ischaemic, diabetic retinopathy and also in *H. pylori* induced upper gastrointestinal disorders and/or extra intestinal diseases, including autoimmune and neurodegenerative ones. Glaucoma is associated with some autoimmune and neuro degenerative disorders such as, Sjogren's syndrome, Guillain-Barre syndrome, Alzheimer's disease or Parkinson's disease characterized by apoptotic loss of specific populations of neurons.

**Helicobacter pylori infection and the risk for open angle glaucoma**

An association between *H pylori* infection and glaucoma was first suggested by Kountouras *et al* (2001) in Greece who in their further studies concluded that *H pylori* eradication may positively influence glaucoma parameters and suggested a possible causal link between *H pylori* and glaucoma (Kountouras et al., 2002). Galloway *et al* (2003) on the other hand, in a study supported by the Glaucoma Research Society of Canada, however, refuted any such association. Thus, the reports on such association between *H. pylori* and glaucoma are conflicting (Ozturk *et al* 2000; Kountouras *et al* 2004; Kurtz *et al* 2008; Deshpande *et al* 2008). For instance, Kountouras *et al* (2002) reported that Greek physicians have tried to find out whether glaucoma patients are infected with *H. pylori* at the same rate as those without the disease. For these two years trials, they included 41 patients (aged 45-70) with chronic open-angle glaucoma to participate in this study, along with 30 age-matched controls (aged 44-70) with no glaucoma. During these two years trials, the glaucoma patients were treated with topical drugs (but no oral drugs) for their condition. The tissue samples collected from the participants' stomachs at the outset of the study revealed that the glaucoma patients were almost twice as likely to be infected with *H pylori* as the controls: 88% vs. 47% suggesting that people infected with *H pylori* are much more likely to become victims of glaucoma than uninfected individuals. This study however raised an obvious question: If someone has glaucoma and is simultaneously infected with *H. pylori,* can eradication of the bacterium meliorate the outlook? Yes, as reported by Kountouras *et al* (2002) who suggested that eradication of *Helicobacter pylori* may be beneficial in the management of chronic open-angle glaucoma. In a similar study, the positivity of *H pylori* detected by $^{13}$C-urea breath test was found significantly higher in patients with glaucoma (54.2%) than in control participants (20.8%). The odds ratio for association between *H pylori* and POAG was 4.49, and the 95% confidence interval ranged from 1.26-16.01. The mean visual field defect and cup-disc ratio of patients with glaucoma did no show any significant variations among *H pylori*-positive or *H pylori*-negative patients (Hong *et al* 2007). This study further consolidated the fact that *H pylori* infection might be associated with open angle glaucoma in patients.

Yet in a prospective, non-randomized and comparative study, Kountouras *et al* (2001) investigated 32 patients with primary open angle glaucoma, nine patients with pseudo exfoliation glaucoma and 30 age matched anaemic control participants. Standard upper gastrointestinal endoscopy was performed on all the participants to identify evidence of macroscopic abnormalities. Three biopsy specimens were obtained from the antral region of the stomatch within two centimeter of the pyloric ring, and three specimens were obtained from the fundus. One biopsy specimen from each site was used for rapid urease slide testing of *H. pylori* infection (CLO test: Delta West) and the other two biopsy specimen were placed in 10% formalin and submitted for histologic examination. Before endoscopy, venous blood was drawn from each patient of serologic testing of *H pylori* immunoglobulin (Ig) G antibodies. The sera stored at-20$^{o}$C were used to assay IgG antibodies against *H pylori* employing enzyme linked immunosorbent assay (ELISA) while saliva samples were used to assess urease activity by CLO test. The prevalence of *H pylori* infection was found as 87.5% in the POAG patients, 88.9% in the PEG patients and 46.7% in the anaemic control participants. Furthermore, the urease test revealed 71.9, 77.8 and 46.7% population of *H pylori* in patients with POAG, PEG and the anaemic control participants, respectively. While in saliva of POAG, PEG and anaemic control, the density of *H. pylori* was 37.5, 55.6 and 30%, respectively a detected by urease test. A significantly increased level of IgG anti- *H pylori* antibodies (>10 U/ml) was observed in 68.3% of the glaucomatous patients, and in 30% of the anaemic control participants. While comparing the serum level with control, the mean IgG anti- *H pylori* value was also significantly higher in glaucoma patients (17.03+18.1 vs. 35.6+31.1 U/ml) , 68.8% in the subgroup of POAG, and in 66.7% of the PEG subgroup. This finding thus validated a strong relationship between *H pylori* infection and glaucoma. The authors however, recommended further rigorously controlled epidemiologic studies to confirm whether this association was causal or coincidental. In a follow up study, Kountouras *et al* (2003) obtained an acceptable *H pylori* eradication rate of 83% by using a triple eradication regimen of omeprazole, clarithomycin and ampicillin. At the two years clinical end point, open angle glaucoma parameters like, IOP and visual field parameters were improved in the subgroup of patients where *H pylori* eradication was successful for both IOP and visual field parameters, but not in other patients. Thus it was concluded that *Hpylori* eradication may positively influence glaucoma parameters and a possible causal link between *H pylori* and glaucoma was suggested. In a similar study, supported by the Glaucoma Research Society of Canada, Mickelberg *et al* (2003) also noted a higher prevalence of *H pylori* infection in patients with open angle glaucoma (26.0%) than in controls (20.2%).

On the contrary, Galloway et al. (2003) while investigating the frequency of exposure to *Helicobacter pylori* infection in glaucoma patients [38 patients with primary open-angle glaucoma (POAG), 19 with normal pressure glaucoma (NPG), 16 with pseudoexfoliation glaucoma (PXE), and 24 with ocular hypertension (OHT) while ninety-four age-matched participants without glaucoma served as a control population) using ELISA reported that seropositivity for *H pylori* was higher in patients with glaucoma (26.0%) than in controls (20.2%), but this did not achieve statistical significance ($P = 0.46$). A total of 26.3% of POAG patients, 26.3% of NPG patients, 25.0% of PXE patients, and 25.0% of OHT patients were seropositive. This study thus suggests that exposure to *H pylori* infection is not associated with open-angle glaucoma. In a follow up study, Ozturk *et al* (2009) although reported a possible relationship between *H pylori* infection and glaucoma, this infection does not seem to be a causative factor for glaucoma suggesting that further studies are required to clarify this possible relationship.

Despite all the controversies, the association may exist because- (i) both are diseases of older adults (ii) chronic *H pylori* infection may produce systemic disorders involving vascular tone resulting from the release of vasoactive and pro-inflammatory substances (Mendell *et al* 1994: Gasbarrini *et al* 1999) (iii) development of cross-mimicry between endothelial and *H pylori* antigens (Gasbrinni *et al* 1998) (iv) *H. pylori* induces apoptosis in gastric mucosa by the only mechanism reported as a pathway in trabecular meshwork ( Agarwal *et al* 1999) (v) *H pylori* infection is associated with arteriosclerosis induced increase in platelet activation and aggregation (Markus and Mendall *et al* 1998) (vi) pseudo-exfoliation specimens share common histopathology features associated with *H pylori* infected gastric ulcers (Bode *et al* 1991) and (vii) producing reactive oxygen metabolites such as, lipid peroxidase. Such reactive oxygen metabolites may be involved in the pathophysiology of glaucoma (Koutouras 2001).

**H pylori infection and induction of apoptosis in glaucoma**

*H pylori* infection may influence the pathophysiology of glaucoma by promoting platelet and platelet leukocyte aggregation, releasing pro-inflammatory and vasoactive substances such as, cytokines (IL-1,IL-6, IL-8, IL-10, IL-12, TNF-,á interferon- g), eicosanoids (leukotrienes, prostaglandins) and acute phase proteins (fibrinogen, c reactive protein) (Fu *et al* 1999). These substances are involved in a number of vascular disorders including glaucoma, stimulating mono-nuclear cells to induce a tissue factor like pro-coagulant activity that converts fibrinogen in fibrin, causing the development of cross mimicry between endothelial and *H pylori* antigens. This cross mimicry produces reactive oxygen metabolites and circulating lipid peroxides and influences the apoptotic process that may also be involved in the pathogenesis of glaucomatous neuropathy. In particular, increased endothelin, a potent constrictor of arterioles and venules, nitric oxide (NO) and inhibitor of nitric oxide synthase (NOS) levels are known to be associated with *H pylori* infection (Slomiany *et al* 2000). Of these, endothelin-1 induces vasoconstriction of anterior optic nerve vessels and decrease aqueous humor outflow (Orgul *et al* 1998; Haefliger *et al* 1999) while nitric oxide modulation of vascular tone in the ophthalmic artery may lead to glaucomatous damage. Moreover, nitric oxide, a rapidly diffusing gas and a potent neurotoxin may also facilitate the apoptotic death of retinal ganglion cells in glaucomatous optic neuropathy. In this context, the reported evidence suggests that retinal ganglion cell apoptosis is attenuated by neutralizing antibodies against TNF-á or by selective inhibitors of inducible NOs supports the role of nitric oxide neurotoxicity in glaucoma. This in turn suggests that the inhibitions of TNF á or the inducible isoform $NOS_2$ may provide novel therapeutic targets for neuro-protection in the treatment of glaucomatous optic neuropathy. Similarly, *H pylori* induced cytokines, such as TNF-á, may exert apoptotic and/or anti apoptotic effects thereby playing a pivotal role in the pathogenesis of extra-intestinal vascular disorders like, migraine, Raynaud's phenomenon, ischaemic heart disease, and possibly glaucoma.

Auto-antibodies directed toward retinal antigens may facilitate apoptotic cell death in glaucoma patients. Similarly, gastric autoimmunity is also well reported in patients with *H pylori* infection associated with induction of auto-antibodies that cross react with the gastric mucosa. Moreover, molecular mimicry of host structures by the lipo-polysaccharides of *H pylori* is thought to be connected with development of auto immune sequeale (auto antibodies) in neuropathies (such as Guillain-Barre Syndrome or possibly glaucoma), that induce apoptotic damage of neurons. This theory is supported by the findings of Kountouras *et al* (2003) who reported that the titer of anti *H pylori* IgG antibodies in aqueous humour of patients with glaucoma may reflect the severity of glaucomatous damage.

The heat shock proteins (Hsps), especially Hsp 60 or Hsp 70 expressed by *H. pylori* may represent a major target antigen involved in the molecular mimicry causing an auto-reactivity between *H pylori* and host's immune gastric tissue (Gobert *et al* 2004). Recently, heat shock proteins are being considered as a promising tool for submit vaccines efforts to rule out the possibility or to identify that Hsps of *H pylori* can trigger autoimmune mechanism leading to autoimmune diseases in case of glaucoma. In this context, there is evidence that have suggested the presence of increased serum auto-antibodies against Hsp27 and its role in pathogenetic importance. For instance, exogenously applied Hsp 27 antibody enters to neuronal cells in human retina by an endocytic mechanism through parapapillary defects of the outer blood-retina barrier. After internalization, Hsp27 antibody facilitates apoptotic cell death in retinal ganglion cell layer. The observation that the protective activity of native Hsp27 can be modulated by auto-antibodies to Hsp27, and the apoptotic cell death of retinal ganglion cells can be induced by intravitreal administration of purified anti-neuron specific enolase antibody, may provide a rationale for novel immune-based strategies to modulate apoptotic cell death in glaucoma.

## Conclusion

It can therefore, be speculated that variable apoptotic signals induced by *H pylori* appear to influence the glaucomatous optic neuropathy, thereby indicating an underlying dysregulation of apoptosis as a patho-physiological link between *H pylori* infection and glaucoma. Since glaucoma is currently the second most common reason of blindness around the world and that *H pylori* is a prevalent infection distributed widely, extensive research is urgently required to elucidate as to how exactly abnormal regulation of *H pylori* mediated apoptosis does influence the pathogenesis of glaucoma.

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