

Further data on the association between *Helicobacter pylori* infection and primary open-angle glaucoma

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We herein wish to provide data additional to those reported in our previous review (Tsolaki et al¹) concerning the association between *Helicobacter pylori* (*H. pylori*) infection and primary open-angle glaucoma. These data were not available in the time period when the review paper was submitted and accepted for publication, and we believe that they need to be added because they further reinforce this association.

In our new study published this year,² we show for the first time the existence of *H. pylori* bacteria in the trabeculum and iris specimens of glaucoma patients, thereby further supporting the role for *H. pylori* infection in the pathophysiology of primary open-angle glaucoma. Specifically, the study included 51 consecutive patients who underwent trabeculectomy for primary open-angle glaucoma not responsive to topical antiglaucoma therapy. The presence of *H. pylori* was established by upper gastrointestinal endoscopy and histology, or by a urea breath test in eight patients who either were deemed not suitable endoscopy candidates or refused to undergo endoscopy.

All the patients underwent a surgical trabeculectomy procedure to their eyes, during which tissue samples from the trabeculum, conjunctiva, and iris were immediately obtained, placed in tubes containing 10% formalin, and submitted for histological examination. These specimens were stained using the Cresyl fast violet method (for detection of *H. pylori* organisms). In five patients, for whom gastric *H. pylori* histology was positive, we managed to identify *H. pylori* bacteria in the trabeculum and iris specimens histologically with Cresyl fast violet stain for the first time. The reason why *H. pylori* was not found in the trabeculum and iris of all primary open-angle glaucoma patients who tested positive for *H. pylori* status could be explained, apart from the absence of *H. pylori* in the eye, by the very small size of the sample of tissue obtained and submitted for histopathology during trabeculectomy, or possibly by standard local antisepsis prior to surgery. Despite the small number of cases, the findings of this study are important because *H. pylori* bacteria have been detected for the first time in the trabeculum and iris of patients with primary open-angle glaucoma, confirming that the bacterium is present locally, and is possibly directly implicated in glaucomatous damage.

In a second study just accepted for publication,³ we obtained biopsy specimens at upper gastrointestinal endoscopy from 43 patients with primary open-angle glaucoma, which were then evaluated for the presence of *H. pylori*, for expression of genes involved in cell proliferation and apoptosis (Ki-67, p53, Bcl-2), and for indices of cellular immune surveillance (T lymphocytes [TLs] and B lymphocytes [BLs]). Of the

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43 patients eligible for upper gastrointestinal endoscopy, 90.7% tested positive for *H. pylori* infection. Ki-67 was positively expressed in 81.25% of patients with *H. pylori* infection and in one patient without *H. pylori* infection. p53 was positively expressed in 31.25% of patients with *H. pylori* infection but not in those without *H. pylori* infection. Bcl-2 was positively expressed in 68.75% of patients with *H. pylori* infection and in one patient without *H. pylori* infection. Ki-67, p53, and Bcl-2 were overexpressed in 19%, 25%, and 37.5%, respectively, of patients with *H. pylori* infection, but none was overexpressed in the patients without *H. pylori* infection. The TL marker was positively expressed in all patients with *H. pylori* infection and in the one patient without *H. pylori* infection. The BL marker was positively expressed only in one patient with *H. pylori* infection. Therefore, our forthcoming article provides further evidence that the *H. pylori*-induced oncogenes, Ki-67, p53 and Bcl-2, as well as TL markers are involved in cell proliferation and apoptotic pathways, thereby contributing to glaucomatous neuropathy, with oncogenic potential. In this respect, and apart from the apoptotic processes involved in the pathophysiology of glaucomatous neuropathy, recent experimental data indicate that cell proliferation rather than astrocyte hypertrophy characterizes early pressure-induced optic nerve head injury, and the optic nerve head is the principal site of initial axonal injury in glaucoma. Furthermore, at the eye level, Ki-67 has been used as an index of melanoma proliferation and also as an index showing response to treatment with agents that inhibit the proliferation of Tenon's fibroblasts, decreasing excessive scarring after trabeculectomy.²

Specifically, we have also very recently provided an overview of the various pathophysiological mechanisms underlying the association between *H. pylori* infection and primary open-angle glaucoma⁴ which include: promoting platelet and platelet-leukocyte aggregation, also involved in the pathophysiology of glaucoma; releasing proinflammatory and vasoactive substances, including cytokines (interleukins-1, -6, -8, -10, and -12, tumor necrosis factor alpha [TNF- α], interferon-gamma), eicosanoids (leukotrienes, prostaglandins) and acute-phase proteins (fibrinogen, C-reactive protein) involved in vascular disorders and glaucoma; stimulating mononuclear cells to induce tissue factor-like procoagulant activity that converts fibrinogen into fibrin; causing the development of cross-mimicry between endothelial and *H. pylori* antigens; producing oxidative stress and circulating lipid peroxides; and in particular influencing the apoptotic process, parameters of which may also exert their own effects

in the induction and/or progression of glaucoma and other neurodegenerative disorders (Guillain-Barré syndrome, Alzheimer's disease, Parkinson's disease) associated with both *H. pylori* infection and glaucoma.

Importantly, *H. pylori* infection and glaucoma share the Fas/FasL and mitochondria-mediated apoptotic pathways, thereby suggesting an apoptotic link in the pathophysiology of both diseases. In particular, increased endothelin-1 (a potent constrictor of arterioles and venules), nitric oxide, and inducible nitric oxide synthase levels are associated with *H. pylori* infection. Endothelin-1-induced anterior optic nerve vessel vasoconstriction and vascular tone modulation by nitric oxide in the ophthalmic artery may produce glaucomatous damage. Moreover, nitric oxide, a rapidly diffusing gas, is a potent neurotoxin that may facilitate apoptotic retinal ganglion cell death in glaucomatous optic neuropathy. Support for the consideration of nitric oxide neurotoxicity in glaucoma is provided by experimental evidence demonstrating that retinal ganglion cell apoptosis is attenuated by neutralizing antibodies against TNF- α or by selective inhibitors of inducible nitric oxide synthase, thereby suggesting that the inhibitors of TNF- α or of the inducible isoform (NOS-2) may provide novel therapeutic targets for neuroprotection in the treatment of glaucomatous optic neuropathy.

In addition, systemic *H. pylori*-induced oxidative damage may be the mechanism which links oxidative stress, *H. pylori* infection, and the apoptotic damage to the trabecular meshwork and optical nerve head that results in glaucoma. In this regard, oxidative stress is an essential underlying cause of neuroinflammatory and neurodegenerative diseases, including glaucoma and the blood-brain barrier damage connected to these diseases; oxidative stress activates protein tyrosine kinase and matrix metalloproteinases, resulting in blood-brain barrier dysfunction.⁴

H. pylori infection, by releasing several inflammatory mediators,⁵ could induce breakdown of the blood-brain/blood-ocular barriers, thereby being involved in the pathogenesis of neuropathies, including glaucoma.⁵ For instance, *H. pylori* could indirectly affect the brain through the release of TNF- α acting at a distance; TNF- α is involved in blood-brain barrier disruption through upregulation of matrix metalloproteinases. Furthermore, circulating antibodies for *H. pylori* might also enter the aqueous circulation due to disruption of the blood-brain/blood-ocular barriers, possibly contributing to the pathophysiology of glaucoma; when serum-specific antibodies access the brain, they are capable of killing retinal cells.⁵ Likewise, an influx of *H. pylori*-infected monocytes, owing to defective autophagy

resulting in *H. pylori* replication in autophagic vesicles, through the disrupted blood–brain/blood–ocular barrier, might lead to glaucoma neuropathy. *H. pylori* VacA cytotoxin promotes intracellular survival of the bacterium and modulates host immune responses.⁵ In addition, because the oral cavity might act as a permanent reservoir for *H. pylori*, this bacterium may reach the eye through the nasal cavity, causing ophthalmic pathologies, possibly including glaucoma.⁵

Finally, it is important to note that studies conducted in Korea, China, India, Turkey, and Iran have also reported an association between *H. pylori* infection and glaucoma.²

Disclosure

The authors report no conflicts of interest in this work.

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