**Letters**

*Helicobacter pylori*-Related Impact on Glaucoma Pathophysiology

In their meta-analysis, Zeng et al. showed a significant association between *Helicobacter pylori* infection (HpI) and open-angle glaucoma (OAG) but not pseudoxfoliation glaucoma (PXFG), for which we would like to add our interpretation based on the existing literature, including our own published data. Regarding the pathogenesis of PXFG, an infection appears to be one of the proposed pathogenetic mechanisms. In this respect, by using histology, representing the practical gold standard for HpI diagnosis, we documented for the first time to our knowledge a high prevalence of HpI in OAG and PXFG patients than in controls with mild iron deficiency anemia (IDA). It is important to note that, regarding the mild IDA controls used in our series, the link between Hp and IDA was well supported in the literature; the British Society of Gastroenterology and the recent Maastricht IV guidelines recommend Hp eradication in all patients with unexplained and/or recurrent IDA with a normal esophagogastroduodenoscopy and colonoscopy. Therefore, it was a “disadvantage” for us to use IDA controls, expected to exhibit a high Hp prevalence. However, we believed that it was not ethical to submit healthy subjects for endoscopic and histologic investigation. Nevertheless, the use of such IDA controls appears to reinforce our own results. In addition, apart from OAG, our results also showed significantly greater concentration of anti-Hp-specific IgG in the aqueous humor samples from patients with PXFG than in those from age-matched control cataract patients; a similar picture also was obtained from serum concentration of anti-Hp IgG antibodies. Therefore, it is conceivable that both forms of glaucoma may share a common infectious link. The possibility of an infectious pathogenetic mechanism in PXFG was further implied by an epidemiologic study in Norway, where the prevalence of this condition was significantly more common in spouses with the disease. One consequent study from Iran also showed significantly higher levels of anti-Hp IgG in the aqueous humor of PXFG patients compared to the cataract control group, though relative concerns were raised regarding the methodology of this study. Moreover, one more subsequent study from India showed a trend of nonsignificant greater mean concentration of anti-Hp-specific IgG in the aqueous humor samples from patients with PXFG than in controls (8.87±30.25 vs. 2.65±2.87, *P* = 0.83). Thus, apart from OAG, the possibility of an association between infectious agents, such as HpI, and PXFG, might occur at least in some ethnic subpopulations, including Greek PXFG patients, but additional large-scale relative studies are required to elucidate the aforementioned possibility.

Regarding the possible impact of HpI on glaucoma pathophysiology, the authors mentioned some possible mechanisms that can support the fact that HpI increases the risk of OAG. Adding some further insight on the pathophysiology proposed by the authors, HpI, by releasing some inflammatory mediators (e.g., cytokines and chemokines induced by HpI), could induce blood-brain barrier (BBB)/blood-ocular barrier (BOB) breakdown, thereby being involved in the pathogenesis of neuropa-thies, such as Alzheimer’s disease (AD) and glaucoma, also called “ocular AD.” *Helicobacter pylori* could indirectly affect the brain and other target organs, for example the heart, through the release of numerous cytokines, such as TNF-α acting at a distance; TNF-α is involved in BBB disruption through a mechanism involving matrix metalloproteinases upregulation. Tumor necrosis factor-α and IL-6 (TNF-α is the main trigger for the production of IL-6 by a variety of cells) have important roles in the regulation of the synthesis of other acute phase proteins that are established risk factors for atherosclerosis, such as fibrinogen and factor VIII. These cytokines also have profound effects on lipid metabolism directly at the site of the atherosclerotic lesion but could influence the atheroma process through blood circulating levels, distant production of cytokines, or through stimulating circulating white blood cells to produce them, thereby contributing to BBB/BOB disruption and pathogenesis of heart and brain neurodegenerative diseases including glaucoma.

Furthermore, Hp antibodies circulating in the bloodstream can enter the aqueous circulation due to BOB disruption possibly contributing to glaucoma development and progression; when serum-specific antibodies access the brain, they are capable of killing retinal cells, thereby contributing to glaucoma pathologies. Likewise, an influx of Hp-infected monocytes, owing to defective autophagy resulting in Hp replication in autophagic vesicles, through the disrupted BBB/BOB might lead to glaucoma neuropathy.

In this regard, Hp VacA cytotoxin promotes intracellular survival of the bacterium and modulates host immune responses; Hp VacA also exhibits chemotactic activities to the bone marrow–derived mast cells (BMDMCs) and induces BMDMCs to produce proinflammatory cytokines, including the mentioned TNF-α; BMDMCs reside adjacent to blood and lymphatic channels, mainly under epithelial surfaces including the BBB and gastrointestinal tract.

*Helicobacter pylori* stimulates mast cells directly or via gastrin induction, and mast cells are actively involved in the pathogenesis of Hp-associated pathologies. Apart from activated mast cells, VEGF, IL-8, chymase, or tryptase (a serine endopeptidase released by mast cells) and mast cell growth factor linked to fibrinogen, secreted under stress, to release mediators, including histamine, IL-8, tryptase, and VEGF which disrupt the BBB/BOB leading to brain pathologies. Moreover, human defensins can penetrate BBB and also might contribute to Hp-related brain pathophysiology by modulating innate and adaptive immune system responses; when Hp accesses the brain, it may trigger defensin-related dendritic cells maturation and activation leading to proinflammatory cytokine release by effector T cells, thereby promoting neuronal cell injury and death. Finally, since the oral cavity might act as Hp permanent reservoir, this bacterium may reach the eye through the nasal cavity, causing ophthalmic pathologies, possibly including glaucoma. Hp, through oral–nasal–olfactory pathway, might also access brain, thus leading to the development of degenerative diseases via abnormal regulation of innate and adaptive immune responses possibly mediated, at least partly, by defensins’ inappropriate stimulation. Therefore, Hp’s intranasal route appears to explain, at least partly, the demonstrated presence of Hp in tissue samples obtained during trabeculectomy in our series; quite recent data confirmed the hypothesis that neurodegenerative diseases, such as dementia and glaucoma are linked to each other and to HpI. Certainly, all the aforementioned speculations warrant clarification and confirmation by future relative studies.

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