Commentary

Comments to the Editor concerning the paper entitled "The microbiome and ophthalmic disease" by Baim et al.

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Baim et al.[1] in their informative narrative review demonstrated the existing piece of evidence linking microbiome and ocular disease. Apart from other pathogens, *Helicobacter pylori* (*Hp*) was associated with primary open angle glaucoma (POAG) and diverse interesting mechanisms were suggested, which could interpret its potential virulence.

Since both *Hp* infection (*Hp*-I) and glaucoma appear to be large worldwide health burdens (*Hp*-I affects approximately half of the world population[2] and there were around 4.4 billion individuals with *Hp*-I worldwide in 2015; glaucoma is the second leading cause of irreversible blindness, and there are 64.3 million individuals with glaucoma globally[3]), we wish to add further relevant information regarding the *Hp*-I involvement in the pathophysiology of glaucoma and other ocular pathologies. Specifically, beyond its very well-documented involvement to gastric ulcer and adenocarcinoma, *Hp* appears to have pleiotropic extra-gastric effects.[2,4] Among others, emerging evidence supports the association between *Hp* and central nervous system pathologies and particularly Alzheimer's disease (AD). Likewise, *Hp*-I has been implicated in the pathogenesis of glaucoma and accumulating data support this causative hypothesis.[5–8] The latter is known bibliographically as "ocular AD," since both modalities share common pathophysiologic mechanisms.[2]

As soon as 2001, our research team revealed, by using the gold standard of histologic substantiation, a high *Hp-I* prevalence in patients with POAG and pseudoexfoliation glaucoma (PEG).[9] Later on, we reported[10] a positive effect on POAG progression after *Hp* eradication with accompanying reduction in intraocular pressure and improvement of visual field parameters, study also mentioned by the authors.[1] It is important to note that the majority of our glaucoma patients, particularly the subgroup of patients in whom the *Hp* eradication treatment was unsuccessful, exhibited chronic atrophic gastritis.[9,10] In this respect, relative studies reported that *Hp*-related chronic atrophic gastritis or atrophic gastritis per se results in malabsorption of vitamin B-12 and folate, which leads to the failure of methylation by 5-methyl-tetrahydrofolic acid and, thus, to homocysteine (Hcy) accumulation. Subsequently, elevated Hcy concentrations can trigger endothelial dysfunction and vascular oxidative injury involved in the pathophysiology of neurodegenerative disorders including dementia, AD and glaucoma.[11–13] Endothelial injury and vascular dysregulation play a role in glaucomatous optic nerve atrophy pathogenesis, and hyperhomocysteinemia is a risk factor for endothelial dysfunction and is associated with both POAG and PEG.[13] Moreover, augmented Hcy concentrations observed in the plasma and aqueous humor of POAG patients can induce oxidative stress damage in human trabecular meshwork cells, thereby signifying that Hcy could be a potential treatment target in POAG patients.[14]

Likewise, we showed that specific *Hp*-immunoglobulin G antibody concentration in the aqueous humor of POAG and PEG patients was increased, and there was a correlation of this concentration to the degree of vertical cupping, possibly reflecting the severity of glaucomatous damage.[15] Additionally, we detected, for the first time, *Hp* microorganisms in iris and trabeculum of POAG patients.[16] Relevant data from different countries including Korea, Turkey, China, Iran and India, using serology or the ^{13}C-urea breath test, support a causative relationship.[8] However, as mentioned by the authors,[1] the *Hp* involvement in glaucoma pathogenesis remains controversial with wide variability of diagnostic criteria among existing studies as well as Israel groups reporting no significant association with either pathogenic or non-pathogenic strains of this organism, by using serology.[17] Nevertheless, concerns have arisen regarding the methodology, selection of patient groups, and claims considered by

the aforementioned Israel series,[18] and thus further research is needed.

Apart from hyperhomocysteinemia, *Hp*-I might affect the pathophysiology of POAG by several additional mechanisms. For example, *Hp*-I can induce nitric oxide synthase (iNOS) expression and nitric oxide (NO) overproduction derived from iNOS; NO is a rapidly diffusing gas and in sufficient concentrations is a potent neurotoxin that may facilitate the apoptotic death of retinal ganglion cells in the pathophysiology of glaucomatous optic neuropathy.[7] Abnormalities in regulation of apoptosis appear to influence the pathophysiology of both *Hp*-I and glaucoma. Two major pathways of apoptosis that include Fas/Fas ligand (Fas or membrane death receptor)-mediated and mitochondria-dependent signaling for cell degradation appear to play crucial roles in the pathogenesis of glaucoma and *Hp*-induced pathologies, thereby suggesting an apoptotic link in the pathophysiology of both diseases.[19] Moreover, *Hp*-I might induce blood–brain barrier (BBB)/blood–ocular barrier (BOB) breakdown by releasing the several inflammatory mediators, thereby contributing to the pathogenesis of glaucoma and other neuropathies. For example, *Hp* could indirectly signal brain through the production and distant action of TNF-α; the latter is involved in BBB disruption through matrix metalloproteinases' upregulation.[20] Moreover, *Hp*-induced vacuolating cytotoxin A exhibits chemotactic activities to the bone marrow-derived mast cells (BMD-MCs) and induces BMD-MCs to produce proinflammatory cytokines involved in the BBB disruption. In this respect, TNF-α alone, or in combination with other cytokines, induces permeability of the blood–retinal barrier (BRB)[21] and BRB breakdown is implicated in ophthalmic diseases including POAG;[22] BRB permeability renders circulating mediators, such as endothelin-1 (ET-1), a potent constrictor of arterioles and venules, direct access to optic nerve head and to adjacent retinal tissue, thereby resulting in vasoconstriction observed in the peri-papillary retinal vessel in glaucoma patients.[7,23] In this respect, increased ET-1 and NO are associated with *Hp*-I and ET-1-produced vasoconstriction of the anterior optic nerve vessels and NO modulation of vascular tone in the ophthalmic artery might promote glaucomatous damage;[7] ET-1 and NO are significantly raised in the aqueous humor of patients with POAG, thereby possibly involving in POAG pathophysiology.[24]

Furthermore, circulating antibodies against *Hp* might also invade the aqueous circulation due to aforementioned BOB/BRB disruption, thus potentially being implicated in glaucomatous and neuropathy pathophysiology; once serum-specific antibodies of glaucoma patients enter the brain, they are known to have deadly properties against retinal cells.[15] Moreover, circulating monocytes with defective autophagy may ingest *Hp*, which later replicates in autophagic vesicles and reaches the central nervous system through disrupted aforementioned barriers (the so-called Trojan horse theory) and might lead to POAG and related pathologies like AD. Finally, once oral cavity serves as *Hp* reservoir, the microorganism might reach the ophthalmic tissues and brain through nasal cavity and the so-called olfactory pathway, causing thus POAG and neurodegenerative pathologies.[2,8]

Of particular interest is the evidence, that an increasing number of ocular pathologies, beyond POAG are associated with *Hp-I.* Central serous chorioretinitis and blepharitis belong to this category, and evidence is significantly strengthened by relevant positive systematic reviews with meta-analysis.[25–27] In this respect, *Hp* may reach the eye through the aforementioned nasal cavity, possibly causing, apart from blepharitis, and dacryostenosis (DS).[28] Relative evidence indicates that ascending nasal inflammation or descending ocular inflammation play a role in DS development; ascending agents (i.e. pepsin) of gastroesophageal reflux (GER) may induce local swelling of the nasolacrimal duct mucosa, which might progress to fibrosis and chronic inflammation ultimately resulting in the occurrence of DS; and deficiency of trefoil factor family (TFF) peptides that regulate the human lacrimal system, may also contribute to DS development. Moreover, although other antimicrobial peptides (defensins) appear to exhibit therapeutic effects in dacryocystitis, caution is needed since defensins are also known for their ability to induce fibrin formation and cell proliferation, critical elements in DS; in particular, human-beta defensin (HBD)-2 is detected in the lacrimal passage in the presence of bacterial dacryocystitis,[28] and the detection of *Hp* in lacrimal secretions by PCR indicates the existence of a number of mechanisms for *Hp* transmission to lacrimal secretions.[29] Our own data reveal that: *Hp*-I is involved in GER disease pathophysiology[30] and the ophthalmic tissue *Hp* bacteria,[16] beyond other eye pathologies, could also induce DS, by releasing diverse proinflammatory cytokines, thereby contributing to the descending ocular inflammatory process. Furthermore, *Hp* significantly upregulates HBD-2 expression, which, as a proinflammatory agent, is implicated in *Hp*-related inflammatory disorders and decreases TFF protein expression causing damage, and thus further contributing to DS pathophysiology.[28]

Taken all together, it seems that *Hp* has "gained ground" over the last years, as independent data from different research teams and countries suggest a causative role with mechanistic interpretations, rather than a random coincidence–coexistence. However, further large-scale studies are required, before a consensus regarding ophthalmic pathologies and *Hp* can be reached.

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REFERENCES

1. Baim AD, Movahedan A, Farooq AV, Skondra D. The microbiome and ophthalmic disease. *Exp Biol Med*. Epub ahead of print 21 Nov 2018. DOI: 10.1177/1535370218813616
2. Doulberis M, Kotronis G, Thomann R, Polyzos SA, Boziki M, Gialamprinou D, Deretzi G, Katsinelos P, Kountouras J. Impact of *Helicobacter pylori* on Alzheimer's disease: what do we know so far? *Helicobacter* 2017;**23**:e12454
3. Song P, Wang J, Bucan K, Theodoratou E, Rudan I, Chan KY. National and subnational prevalence and burden of glaucoma in China: a systematic analysis. *J Glob Health* 2017;**7**:79–80
4. Franceschi F, Gasbarrini A, Polyzos SA, Kountouras J. Extragastric diseases and *Helicobacter pylori*. *Helicobacter* 2015;**20**:40–6
5. Kountouras J, Zavos C, Deretzi G. Primary open-angle glaucoma. *N Engl J Med* 2009;**360**:2679; author reply 2679–80
6. Kountouras J, Zavos C, Sakkias G, Deretzi G, Venizelos I, Arapoglou S, Polyzos SA. *Helicobacter pylori* infection as a risk factor for both primary open-angle glaucoma and pseudoexfoliative glaucoma in Thessaloniki Eye Study. *Am J Ophthalmol* 2011;**152**:1079–80
7. Kountouras J, Zavos C, Chatzopoulos D. Primary open-angle glaucoma: pathophysiology and treatment. *Lancet (London, England)* 2004;**364**:1311–2
8. Kountouras J, Deretzi G, Gavalas E, Zavos C, Polyzos SA, Kazakos E, Giartza-Taxidou E, Vardaka E, Kountouras C, Katsinelos P, Boziki M, Giouleme O. A proposed role of human defensins in *Helicobacter pylori*-related neurodegenerative disorders. *Med Hypotheses* 2014;**82**:368–73
9. Kountouras J, Mylopoulos N, Boura P, Bessas C, Chatzopoulos D, Venizelos J, Zavos C. Relationship between *Helicobacter pylori* infection and glaucoma. *Ophthalmology* 2001;**108**:599–604
10. Kountouras J, Mylopoulos N, Chatzopoulos D, Zavos C, Boura P, Konstas AGP, Venizelos J. Eradication of *Helicobacter pylori* may be beneficial in the management of chronic open-angle glaucoma. *Arch Intern Med* 2002;**162**:1237–44
11. Kountouras J, Gavalas E, Boziki M, Zavos C. *Helicobacter pylori* may be involved in cognitive impairment and dementia development through induction of atrophic gastritis, vitamin B-12-folate deficiency, and hyperhomocysteinemia sequence. *Am J Clin Nutr* 2007;**86**:805–6
12. Fu Y, Wang X, Kong W. Hyperhomocysteinaemia and vascular injury: advances in mechanisms and drug targets. *Br J Pharmacol* 2018;**175**:1173–89
13. Jünemann A, Rejdak R, Hohberger B. Stellenwert vom homocystein beim glaukom. *Klin Monbl Augenheilkd* 2018;**235**:163–74
14. You ZP, Zhang YZ, Zhang YL, Shi L, Shi K. Homocysteine induces oxidative stress to damage trabecular meshwork cells. *Exp Ther Med* 2018;**15**:4379–85
15. Kountouras J. *Helicobacter pylori*: an intruder involved in conspiring glaucomatous neuropathy. *Br J Ophthalmol* 2009;**93**:1413–5
16. Zavos C, Kountouras J, Sakkias G, Venizelos I, Deretzi G, Arapoglou S. Histological presence of *Helicobacter pylori* bacteria in the trabeculum and iris of patients with primary open-angle glaucoma. *Ophthalmic Res* 2012;**47**:150–6
17. Kurtz S, Regenbogen M, Goldiner I, Horowitz N, Moshkowitz M. No association between *Helicobacter pylori* infection or CagA-bearing strains and glaucoma. *J Glaucoma* 2008;**17**:223–6
18. Kountouras J, Zavos C, Katsinelos P, Grigoriadis N, Deretzi G, Tzilves D. Greek and Israeli Patterns of *Helicobacter pylori* infection and their association with glaucoma: similarities or diversities? *J Glaucoma* 2008;**17**:503–4
19. Kountouras J, Zavos C, Chatzopoulos D. Induction of apoptosis as a proposed pathophysiological link between glaucoma and *Helicobacter pylori* infection. *Med Hypotheses* 2004;**62**:378–81
20. Kountouras J, Boziki M, Polyzos SA, Katsinelos P, Gavalas E, Zeglinas C, Tzivras D, Romiopoulos I, Giorgakis N, Anastasiadou K, Vardaka E, Kountouras C, Kazakos E, Giartza-Taxidou E, Deretzi G, Dardiotis E, Kotronis G, Doulberis M. The emerging role of *Helicobacter pylori*-induced metabolic gastrointestinal dysmotility and neurodegeneration. *Curr Mol Med* 2017; published online Dec 18. 2017;17:389–404
21. Van der Wijk AE, Vogels IMC, Van Noorden CJF, Klaassen I, Schlingemann RO. TNFα-induced disruption of the blood-retinal barrier in vitro is regulated by intracellular 30'50'-cyclic adenosine monophosphate levels. *Invest Ophthalmol Vis Sci* 2017;**58**:3496–505
22. Gu X, Fliesler SJ, Zhao YY, Stallcup WB, Cohen AW, Elliott MH. Loss of caveolin-1 causes blood-retinal barrier breakdown, venous enlargement, and mural cell alteration. *Am J Pathol* 2014;**184**:541–55
23. Grieshaber MC, Flammer J. Does the blood-brain barrier play a role in glaucoma? *Surv Ophthalmol* 2007;**52**:17998035
24. Ghanem AA, Elewa AM, Arafa LF. Endothelin-1 and nitric oxide levels in patients with glaucoma. *Ophthalmic Res* 2011;**46**:98–102
25. Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M. *Helicobacter pylori* and extragastric diseases: a review. *World J Gastroenterol* 2018;**24**:3204–21
26. Bagheri M, Rashe Z, Ahoor MH, Somi MH. Prevalence of *Helicobacter pylori* infection in patients with central serous chorioretinopathy: a review. *Med Hypothesis, Discov Innov Ophthalmol J* 2017;**6**:118–24
27. Liu B, Deng T, Zhang J. Risk factors for central serous chorioretinopathy: a systematic review and meta-analysis. *Retina* 2016;**36**:9–19
28. Kountouras J, Zavos C, Polyzos SA, Romiopoulos I, Stergiopoulos C, Tsiaousi E, Deretzi G, Giartza-Taxidou E, Vardaka E, Loli E, Kountouras C, Katsinelos P. Is *Helicobacter pylori* the usual suspect behind gastroesophageal reflux disease and dacryostenosis? *Med Hypotheses* 2013;**81**:147
29. Batioglu-Karaaltin A, Saatci O, Akpinar M, Celik MO, Develioglu O, Yigit O, Külekçi M, Akarsubaşı AT. Helicobacter pylori in lacrimal secretions. *Ear Nose Throat J* 2016;**95**:E8–11
30. Doulberis M, Kountouras J, Polyzos SA, Tzivras D, Vardaka E, Kountouras C, Tzilves D, Kotronis G, Boutsikou E, Gialamprinou D, Exadaktylos A, Katsinelos P. Impact of *Helicobacter pylori* and/or *Helicobacter pylori*-related metabolic syndrome on gastroesophageal reflux disease-Barrett's esophagus-esophageal adenocarcinoma sequence. *Helicobacter* 2018;**23**:e12534