Helicobacter pylori infection in a Greek cohort with biliary disease

SIR, In a recent study, Helaly *et al*.[1] showed that *Helicobacter pylori* infection might be an aetiological factor leading to cholecystitis; gastric colonisation with *H. pylori* could be a source for gall bladder infection, and the organism may act as a lithogenic component, especially in the context of pure pigmented gallstones.

In this regard, using serological anti-*H. pylori* IgG antibodies, our own relative data indicate presence of past and/or current *H. pylori* infection in 63/123 (51.2%) patients (64 females, mean age: 63 years) with calcular biliary and pancreatic diseases (cholecystitis/cholangitis and pancreatitis, respectively).[2] Moreover, histological presence of *H. pylori* infection was detected in gall bladder tissue (by cresyl fast violet staining) in 19.3% of Greek cholecystectomised patients (all female).[3]

Although Helaly *et al*. report that the pathways of *H. pylori* penetration into the bile have not been completely explained, they comment that "the possibility is the translocation from the duodenum via Oddi's sphincter and, moreover, bacterial antigen penetration into the portal circulation and lymphatic vessels is also possible".[1]

We also considered the possible pathways of *H. pylori* migration and colonisation in the biliary tract and its potential involvement in inflammatory biliary diseases.[2] Among the risk factors involved in gall bladder stone development, the inflammatory process plays an essential role; chronic biliary inflammation can also contribute to gall bladder cancer.[4]

In this regard, *H. pylori* infection could affect the pathophysiology of gall bladder stone creation and its complications, including cholecystitis, cholangitis, pancreatitis and even biliary cancer by the following mechanisms: i) Releasing large amounts of proinflammatory and vasoactive substances, such as interleukin (IL)-1, IL-6, IL-8 and tumour necrosis factor-α (TNFα) or eicosanoids (leukotrienes, prostaglandins catalysed by cyclo-oxygenase enzymes), and acute-phase proteins (fibrinogen, C-reactive protein) involved in a number of inflammatory diseases,[5] also including gall bladder disorders;[6] *H. pylori* could indirectly affect extragastric tissues possibly including the gall bladder through the release of numerous cytokines such as TNFα acting at a distance;[7] ii) Producing oxidative stress and circulating lipid peroxides[5] also involved in gall bladder disease;[6] for instance, increased production of oxygen and lipoperoxide free radicals and macrophage inflammatory cytokines (IL-6, IL-1α, TNFα) have been reported in blood in gallstone disease female patients, indicating the macrophages' dominant role in the inflammatory and oxidative response during gall bladder stone disease in post-menopausal women;[6] iii) Influencing the apoptotic process,[5] also involved in chronic calculous cholecystitis and gall bladder oncogenesis;[4] seropositivity to *H. pylori* proteins is associated with an increased risk of biliary tract cancer.[8]

Correspondence to: Professor Jannis Kountouras
8 Fanariou St, Byzantio, 551 33, Thessaloniki, Macedonia, Greece
Email: jannis@auth.gr

In addition, *H. pylori*-induced vacA cytotoxin promotes intracellular survival of the bacterium, modulates host immune responses and induces autophagy.[9] Subsequently, *H. pylori*, as an intracellular microorganism, invades and replicates in the cells. The autophagy induction by *H. pylori* is not only found in macrophages but also in dendritic cells (also expressed in acute and chronic cholecystitis)[10] and gastric epithelial cells.[9] The bacterium's residence inside the infected cells will increase its resistance to antimicrobial treatment, avoid neutralisation by anti-*H. pylori* antibodies, impair antigen presentation, and alter the cellular immune response.[9] In turn, the potential influx of activated monocytes infected with *H. pylori* in the gall bladder may lead to gall bladder-related pathologies; a comparable potential influx of activated monocytes infected with *H. pylori* through the disrupted blood-brain barrier, induced by several *H. pylori*-related mediators, in the brain ('Trojan Horse' pathway) might also lead to brain pathologies.[9]

Moreover, comparable to *H. pylori* translocation from the duodenum via Oddi's sphincter to the biliary tract, mentioned by Helaly *et al*.,[1] this bacterium may reach the brain through the oral cavity (which appears to act as a permanent reservoir for *H. pylori*)-nasal cavity-olfactory neuroepithelium pathway, causing central nervous system pathologies.[11]

Therefore, *H. pylori* eradication may have a positive impact on *H. pylori*-related gall bladder and other tissue pathologies. As there is lack of literature showing any demonstrable evidence to support the aforementioned *H. pylori*-related mechanisms involved in the pathophysiology of gall bladder diseases, large-scale studies are necessary to elucidate these fields.

J. Kountouras, E. Tsiaousi, S. Trigonis, C. Zavos, G. Kouklakis
Department of Gastroenterology
Second Medical Clinic
Aristotle University of Thessaloniki
Ippokration Hospital
Thessaloniki
Macedonia
Greece

References

1 Helaly GF, El-Ghazzawi EF, Kazem AH, Dowidar NL, Anwar MM, Attia NM. Detection of *Helicobacter pylori* infection in Egyptian patients with chronic calcular cholecystitis. *Br J Biomed Sci* 2014; **71** (1):13–8.

2 Anastasiadou K, TsiaousiE, Michael S *et al*. *H. pylori* infection in hepatobiliary diseases (in Greek). Proceedings of 13th Hellenic Liver Congress, Rhodes, 2013; P60.

3 Trygonis S, Tsiaousi E, Polyzos S *et al*. Presence of *H. pylori* in gallbladder tissue (in Greek). Proceedings of 13th Hellenic Liver Congress, Rhodes 2013; P54.

4 Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol* 2014; **6**: 99–109.
5 Kountouras J, Zavos C, Chatzopoulos D. Primary open-angle glaucoma: pathophysiology and treatment. *Lancet* 2004; **364** (9442): 1311–2.
6 Shengelia MI, Intskirveli N, Gogebashvili N. Inflammatory markers of gallstones disease in menopausal women. *Georgian Med News* 2012; (208–209): 52–5.
7 Kountouras J, Polyzos SA, Zavos C *et al*. *Helicobacter pylori* might contribute to nonalcoholic fatty liver disease-related cardiovascular events by releasing prothrombotic and proinflammatory factors. *Hepatology* 2014; **60** (4): 1450–1.
8 Murphy G, Michel A, Taylor PR *et al*. Association of seropositivity to *Helicobacter* species and biliary tract cancer in the ATBC study. *Hepatology* 2014; **60** (6): 1963–71.
9 Kountouras J, Deretzi G, Gavalas E *et al*. Aquaporin 4, *Helicobacter pylori* and potential implications for neuromyelitis optica. *J Neuroimmunol* 2013; **263** (1–2): 162–3.
10 Kasprzak AA, Szmyt M, Malkowski W *et al*. Expression of phenotypic markers of mast cells, macrophages and dendritic cells in gallbladder mucosa with calculous cholecystitis. *Pol J Pathol* 2013; **64** (4): 281–9.
11 Kountouras J, Deretzi G, Gavalas E *et al*. A proposed role of human defensins in *Helicobacter pylori*-related neurodegenerative disorders. *Med Hypotheses* 2014; **82** (3): 368–73.