At the present stage of knowledge, the participation of the Helicobacter bacteria in the pathology of liver and the bile tract in humans has not been univocally documented. However, apparent are the premises so as to go on performing the examinations under discussion since the said participation cannot be excluded. If the more direct evidence of the etiologic role of the Helicobacter in the pathology of liver were available, it would create the chances for the more effective treatment of patients than the case has been so far. Cancer commonly derives from the chronic inflammation and infection and in case of hepatocellular carcinoma (HCC), may arise either from local liver derived progenitor cells (LPCs) or bone marrow originated stem cells (BMSCs) and future studies should disclose the role of either type of cells and of inflammatory factors such as generated by Helicobacter infection in the liver pathophysiology.

Key words: liver, biliary tract, hepatic diseases

INTRODUCTION

In recent years, the attention has been drawn to the possible association of Helicobacter infections not only with upper gastrointestinal tract diseases but also with several extra-gastrointestinal diseases e.g. chronic cardiovascular, liver and biliary diseases or colorectal cancer. Helicobacter species have been isolated from the liver samples of a variety of mammals, the role of which has been documented in the etiopathogenesis of chronic hepatitis and various types of liver carcinoma (1-3). It has been demonstrated that these bacteria are resistant to bile acids in contrast to the Helicobacter pylori (H. pylori) which is desintegrated under the influence chenodeoxycholic and deoxycholic acids, the normal components of a human bile (4). Also the possibility exists that bacteria
may undergo the transformation from their spiral form into the spherical pattern in which they are still active metabolically without the ability of multiplying themselves in the culture (5, 6). However, the microscopic methods of examination and the culture fail to identify *H. pylori* in the liver and human bile, but applicable instead are the biochemical, immunohistochemical methods, especially molecular biology techniques. The knowledge of the *H. pylori* contribution in the pathology of the liver and biliary tract diseases in humans is very fragmentary. Demonstrated below are the results of some investigations and opinions on the subject under discussion.

**Hepatic encephalopathy**

The contribution of the *H. pylori* infection of upper gastrointestinal tract in the hepatic encephalopathy results from its synthesizing capability of ammonia because this pathogen expresses highly active urease on its surface and in the periplasma. This enzyme splits the urea, which is amply available in the gastric content and other gastrointestinal secretions, into ammonia and hydrogen carbonate. Its concentration in the portal vein is 5-10 times higher than that in the peripheral blood. The significant amounts of ammonium ion are generated by the liver out of amino acids and proteins. Nevertheless, the ammonium ion is immediately detoxified in the urea cycle. Also the large amounts of ammonium ion (NH$_4^+$) are generated during the muscle action, and the small amounts (30-40 mmol/day) in the kidneys, by the tubular hydrolysis of glutamine (7). In potassium deficiency and alkalosis the renal formation of ammonia is markedly increased. The evidence for a pathogenic role of *H. pylori* infection in hepatic encephalopathy was reported by Suto et al. (8). These authors demonstrated a significant increase in portal and peripheral ammonia levels in *H. pylori*-infected gerbils with *cirrhosis* induced with a choline deficient diet. Nevertheless, these reports were critically analyzed and methodical objections have been raised against them (9). The clinical observations demonstrated the conflicting opinions. Some authors pointed out to the advantageous influence of the eradication therapy on the course of the hepatic encephalopathy (10, 11), but this opinion has not been supported by others (12). The antibiotics used in the eradication therapy do not act in a selective manner on *H. pylori*, but they also restrain the growth of the intestinal bacteria that, as it was mentioned earlier, are the principal “generator” of ammonia. Hence, there are difficulties in the univocal evaluation of the influence of the eradication therapy on the course of the hepatic encephalopathy. The “hepatic *cirrhosis*” can not be an indication of the eradication therapy. However, an ever still wider utilization of the indications specified as the relative ones with respect to the patients with hepatic pathology does not seem to be an excessive abuse. The selection of antibiotics for such instances ought to take into account their hepatic toxicity (for instance, tetracycline) so as to go on respecting the overriding principle of “*primum non nocere*.”
The alcoholic damages of the liver

Alcohol is metabolized in hepatocytes mainly with the participation of an enzyme – the alcohol dehydrogenase (ADH). In addition to this, the microsomal ethanol-oxidizing system (MEOS) and catalase take part in the alcohol metabolism. The gastric isoenzyme of ADH localized in the gastric mucosal cells is responsible for the alcohol metabolism in about 10%. The *H. pylori* decreases the activity of the gastric ADH, thus increasing the “accessibility” of alcohol for the liver. This may create an additional risk factor for the alcoholic damages of the liver (7). It should be emphasized at this point that often administered in upper gastrointestinal diseases cimetidine and ranitidine are also the inhibitors of ADH contained both in the hepatocytes and the gastric mucosal cells.

Chronic liver diseases

The primary sclerosing *cholangitis* (PSC) and the primary biliary *cirrhosis* (PBC) are the cholestatic liver diseases the cause of which is not yet known, but in patients with a genetic predisposition it is actually deemed to be the autoimmune diseases. Nilsson *et al.* (13) identified *H. pylori* in human liver tissue by PCR, hybridization and partial DNA sequencing. Twenty samples from patients with PBC and PSC (11, 9) were positive by PCR for *Helicobacter* genus-specific primers. Nine of these 20 samples were positive for *H. pylori* by two independent PCR assays, based on the sequence of a gene encoding a species-specific 26 kDa surface protein and 16SrRNA, respectively.

A certain surprise was the obtainment of the positive results with the ever still higher percentage of the *Helicobacter* genetic material contained in the biopsy specimens taken from patients with PBC. These observations were confirmed upon larger group of patients (14). Thus, the opinion was expressed that the positive results obtained in this way both with respect to PSC and PBC do not favor the specific role of the bacteria in etiopathogenesis in those disorders. However, it cannot be excluded that they may play a crucial role in the modification of the immunologic response. Therefore, any suggestions pertaining to the participation of the *Helicobacter* in the pathogenesis of cholestatic liver diseases should be approached with necessary care, the more so that some investigations produced somewhat different results (15).

Konturek *et al.* (16) in the group of patients with chronic viral *hepatitis* and liver *cirrhosis* showed the higher percentage of the seropositivity to *H. pylori* than in matched controls, showing 57-68% of *Helicobacter* seropositivity in the *hepatitis* C and B and 83% in the liver *cirrhosis* compared to 50% in the control group. The Polish investigations from Gdansk (17) have demonstrated the similarly high percentage of the seropositive patients with chronic liver diseases ~ 70%. They have also evaluated the incidence of antigens and the *Helicobacter* genetic material simultaneously in the stomach and the liver biopsy specimens with the use of immuno-histochemical and molecular methods. They have
obtained the high percentage of positive results not only in the stomach, but also in the liver, however, the gene encoding cytotoxin protein, CagA, encoded by *H. pylori* gene *cagA* appears to be less apparent in the liver than in the stomach. The same may point out a possible role of Cag A negative *H. pylori*–like organisms in chronic liver diseases.

Recently, Vorobjova et al. (18) analyzed serum antibodies against three *Helicobacter* species – *Helicobacter hepaticus, Helicobacter bilis* and *Helicobacter pullorum* – in patients with various biliary tract and chronic liver diseases, inhabitants of Estonia. With exception of patients with autoimmune *hepatitis*, the increased antibody levels to *Helicobacter bilis* and *Helicobacter hepaticus* were found that could indicate a possible role of enteric *Helicobacter* in the natural course of chronic liver diseases.

**Cholelithiasis**

Of prime significance in the pathogenesis of the cholesterol gallstones – the most apparent disorder, is the supersaturation of the bile with cholesterol. This is not, however, the factor which determines itself the crystallization of cholesterol. The crystallization of cholesterol also necessitates the co-participation of the factors promoting and/or inhibiting the said process. Both the promoters and inhibitors are proteins. The promoters, among other things, include glycoproteins contained in the mucus of the gallbladder, phospholipase C, immunoglobulins (Ig A, Ig M), LDL, transferrin and the other ones (19). Offner et al. (20) ascertained in the gallbladder bile with the patients with *cholelithiasis* the presence of protein with a weight of 130 kDa exhibiting the activity of aminopeptidase and promoting the crystallization of cholesterol. In excess of 90% of the *Helicobacter pylori* strains contains the similar enzyme and the vacuolizing protein toxin encoded by bacteria gene (*vacA*) (21).

As it has already been mentioned earlier, the immunoglobulins contained in the bile promote the crystallization of cholesterol so the presented examinations may speak in favour of a certain participation of the *H. pylori* in the pathogenesis of *cholelithiasis*. The pathways of the *H. pylori* penetration into the bile have not been completely explained. One of the possibilities is the translocation from the duodenum via the Oddi’s sphincter. The examinations performed on animals are indicative of the possible penetration of the bacterial antigens into the systemic circulation with the resulting generation of antibodies, as well as, into the portal circulation and the lymphatic vessels. Upon the uptake of the said bacteria by the liver, the secretion of some out of the liver into the bile is possible. It is also not excluded that the dissolved under the influence of bile molecules constructing the bacterial cell are subjected to the entero-hepatic circulation (20). Similar results were obtained by Apostolov et al. (23), demonstrating in the epithelium cells of the inflammatory gallbladders the presence of cytotoxins CagA and VacA, both encoded by genes of so called toxicity islet of bacteria genome.
Hepatolithiasis is frequent in East Asian countries. In calculi there were found the fragments of the mixed bacterial flora. In excess of the 50% of the instances, the genetic material corresponded to the *H. pylori*. Also, the bile alone taken out of the patients for testing contained the same genetic material which was absent with the patients with the other pathology than hepatolithiasis (24, 25). The authors failed to demonstrate the genetic material of bacteria in the epithelium of the bile ducts, which according to their opinion negates the possibility of the *H. pylori* in the pathogenesis of hepatolithiasis. The different results from the examinations of the patients with hepatolithiasis were obtained by Harada et al (26). They demonstrated in the epithelium of the bile ducts the genetic material of the various species of *Campylobacter*, whereas the presence of the *H. pylori* was only apparent exceptionally.

The hitherto examinations of the participation of the *Helicobacter* and *Campylobacter* species in the pathogenesis of cholelithiasis do not permit the formulation of the univocal conclusions. They do, however, emphasize the need for the further investigations to be acted upon in this respect.

**The primary liver neoplasms**

The infections with the hepatotropic viruses (HBV, HCV) leading to the chronic *hepatitis* and liver *cirrhosis* pose a risk to the development of the primary liver cancer. The observations performed on animals are indicative of the possibility of the participation of bacteria in this process, namely, the *Helicobacter hepaticus* in the hepatic carcinogenesis (27). They have become the basis for the verification of the hypothesis about the possibility of the liver colonization by the unidentified strains of the *Helicobacter* that might possibly lead to the chronic *hepatitis* and liver cancers. The examinations conducted by Avenaud et al. (28) showed the presence of the *Helicobacter* genetic material with closest similarity with the 16SrDNA from *H. pylori*, however, different from it in the livers of the patients with primary hepatocellular carcinoma (HCC) as well as cholangiocarcinoma (CHC). The group of patients under examinations was particular since only in one patient liver carcinoma was associated with *cirrhosis*, whereas the others showed no fibrosis or only mild fibrosis in the underlying liver. Similar results were obtained by Nilsson et al (29) who found the *Helicobacter* genetic material (strictly similar to the *H. pylori*). The other examinations (30, 31) are also convergent with the said examinations. Although the demonstrated examinations are indicative of the possibility of the bacteria participation in the hepatic carcinogenesis, but it is only a hypothesis which does necessitate the further intensified investigations. As HCC develops often following *hepatitis* or in the course of liver *cirrhosis* and the bone marrow stem cells (BMSC) may be engrafted into the damages, inflamed or cirrhotic area of the liver, is a challenge for hepatologists and pathologists to trace the origin and the role of both local and BMSC in both liver
regeneration and development of HCC involving the Helicobacter bacteria as proposed by Houghton’s group (32).

REFERENCES


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