SEROPREVALENCE OF HELICOBACTER PYLORI IN HEPATIC ENCEPHALOPATHY DUE TO VARIOUS LIVER DISEASES

Thesis

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BY

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Abstract

Aims of the study

To find out prevalence of H. pylori in hepatic encephalopathy and to determine correlation between presence of H. pylori and severity of hepatic encephalopathy.

Methodology

One hundred patients (50 patients of chronic liver disease with hepatic encephalopathy and 25 cases chronic of liver disease without hepatic encephalopathy, and 25 healthy controls without any disease) were evaluated for presence of H. pylori by serology (ELISA method).

Results

Seroprevalence of H. pylori infection in the study group (patients of liver disease with hepatic encephalopathy, without hepatic encephalopathy and healthy controls without any disease) was 64% (liver disease with hepatic encephalopathy 74%, liver disease without hepatic encephalopathy 64%, and healthy control 44%). Prevalence and titre of H. pylori were found significantly increasing with the severity of hepatic encephalopathy.

Conclusion

There is a significant association between H. pylori and patients of liver disease with hepatic encephalopathy. There may be a role of anti-H.pylori therapy in patients of hepatic encephalopathy and should be investigated further.

Key wordsH. pylori, Hepatic Encephalopathy, ELISA, Liver Disease.

Acknowledgment

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This work was done by and for the sake of patients. May GOD alleviate their sufferings and accept our honest intentions to dedicate this work for the sake of their own benefit.

Mohamed Abdelkader

List of abbreviations

BabA	Blood group antigen-binding adhesion gen A
Cag A	Cytotoxin associated gene A
Cag PAI	Cytotoxin associated gene pathogenicity island
DNA	Deoxyribonucleic acid
ELISA	Enzyme Llinked Immunosorbant Assay
FHF	Fulminant hepatic failure
GABA	Gamma amino butyric acid
GERD	Gastro-esophageal reflux
H. pylori (HP)	Helicobacter pylori
HE	hepatic encephalopathy
ITP	Idiopathic thrombocytopenic purpura
LOLA	L-ornithine L-aspartate amino acid
MALT	Mucosa associated lymphoid tissue
MEN	Multiple endocrine neuplasia
PCR	Polymerase Chain Reaction
PTBR	Peripheral type benzodiazepine receptor
PUD	Peptic ulcer disease
Vac A	Vaculating cytotoxin A

Introduction

Hepatic encephalopathy is a common and serious complication affecting patients with liver disease. There are various mechanisms for aetiopathogenesis of hepatic encephalopathy. Ammonia is the substance most often incriminated in the pathogenesis of encephalopathy **(Vasconez et al , 1999).**

Normally the ammonia is extracted by the liver; therefore, in liver failure large quantities reach the systemic circulation because of porto-systemic shunting and impaired ureagenesis**. (Renaldi et al, 1997).**

Most of the ammonia is of gut origin where it is produced by bacteria flora. Stomach when infected with H.pylori is an alternative site of ammonia production**. (Ito et al, 1995).**

Helicobacter pylori is the most common bacterial infection in the world, colonizing the stomach of more than 50% of the human population. The discovery of the bacterium has changed the concept of care and management of peptic ulcer disease, mucosa associated lymphomas, gastritis and gastric carcinoma. Although the mode of transmission is not definitely known, person to person contact is suspected **(Howden and Hunt, 1998).**

Across the world, the human upper gastrointestinal tract is commonly infected with H.pylori. This urea splitting bacterium is now considered to be a causal agent in a spectrum of human diseases. However, in the presence of the bacterial urease which has stimulated recent interest into whether H-pylori contribute to the

hyperammonaemia frequently observed in patient with chronic liver disease. Then it was hypothesised that eradication treatment would improve hepatic encephalopathy. **(Le Veen et al, 1994).**

Further studies showed that eradication of H-pylori reduces the blood ammonia level and improves the hepatic encephalopathy. (**Demirturk et al, 2001)**

Shrimali et al, 2001 found that H. pylori seropositivity increases with the severity of hepatic encephalopathy.

AIM OF THE WORK

To study the seroprevalence of H. pylori infection among Egyptian patients with chronic liver diseases including those with hepatic encephalopathy and to determine if any correlation between the presence of H. pylori and the grading of hepatic encephalopathy.

Chapter I - Historical review

Although the association between Campylobacter (helicobacter) pylori and ulcers was discovered by **Robin Warren, 1979** and the organism was cultured by **Barry Marshall,1982** resulting in the seminal publications in the lancetin 1983, the historical origins of its discovery are rooted in the later half of the nineteenth century. It was during this period that the eminent German bacteriologist **Robert koch** proved scientifically that bacteria were the cause of certain diseases **(Modlin and sachs ,1998).**

In Japan, **Kasai and Kobayashi, 1919** of the Kitasato institute reported isolating a spirochete like organism, that might have been Helicobacter felis, from the stomach of dogs and cats, but not that of laboratory animals and demonstrated that when rabbits infected with the spirochetes isolated from dogs or cats were inoculated with the virus fixed, marked hemorrhagic inflammation occurred in the gastric mucosa. They also, demonstrated that spirochetes inoculated into the gastric mucosa of the mouse could be eradicated by the administration of arsaminol (a modern equivalent of arsaminol is thought to be bismuth , a close relative to arsenic) **(Suzuki et al, 2003)** .

Palmer, 1954 investigated spirochetes in human gastric samples using a vacuum tube technique and standard histological techniques, he failed to demonstrate any organism, so he concluded that the results of all previous authors could be best explained as postmortem colonization of the gastric mucosa with oral cavity organisms. So, Palmer's work may thus be credited with the envious distinction of setting back gastric bacterial by further 30 years.

Whitehead et al, 1972 wrote an excellent description of the histology of normal and inflamed human stomachs. His description and classification of gastritis was impressive because he described a specific change in the superficial epithelium that he defined as active. He described the various features of gastritis one after another (**Warren, 2000).**

The bacterium was rediscovered in 1979 by Australian pathologist Robin Warren, who did further research on it with Barry Marshall beginning in 1981; they isolated the organisms from mucosal specimens from human stomachs and were the first to successfully culture them **(McConnell and Harper, 1989).**

In their original paper**, Warren and Marshall** contended that most stomach ulcers and gastritis were caused by colonization with this bacterium, not by stress or spicy food as had been assumed before **(Samuel,1996)**.

The medical community was slow to recognize the role of this bacterium in stomach ulcers and gastritis, believing that no bacterium could survive for long in the acidic environment of the stomach. The community began to come around after further studies were done, including one in which Marshall drank a Petri dish of H. pylori, developed gastritis, and the bacteria were recovered from his stomach lining, thereby satisfying three out of the four Koch's postulates. Marshall's gastritis later resolved without treatment. Marshall and Warren went on to show that antibiotics are effective in the treatment of gastritis. **In 1994**, the National Institutes of Health (USA) published an opinion stating that most recurrent gastric ulcers were caused by H. pylori, and

recommended that antibiotics be included in the treatment regimen **(Blaser, 2005)**.

In 2005, Warren and Marshall were awarded the Nobel Prize in Medicine for their work on H. pylori **(Barry Marshall, 2006).**

Helicobacter is a genus of Gram-negative bacteria possessing a characteristic spiral shape. Some species have been found living in the lining of the upper gastrointestinal tract, as well as the liver of mammals and some birds . The most widely known species of this genus is H. pylori which is a human pathogen and is responsible for most cases of peptic ulcer, chronic gastritis, and stomach cancer. It also serves as the type species of the genus **(Marshall and Warren 1984).**

Helicobacter sp. are able to thrive in the strongly acidic mammalian stomach by producing large quantities of an enzyme called urease, which locally raises the pH from ~2 to a more biocompatible range (pH 6-7). Bacteria belonging to this genus are usually susceptible to antibiotics such as penicillin, are microaerophilic (require small amounts of oxygen), and are fast-moving with multiple flagella (**Pietroiusti and Luzzi, 2005).**

Chapter II – Epidemiology of H. pylori

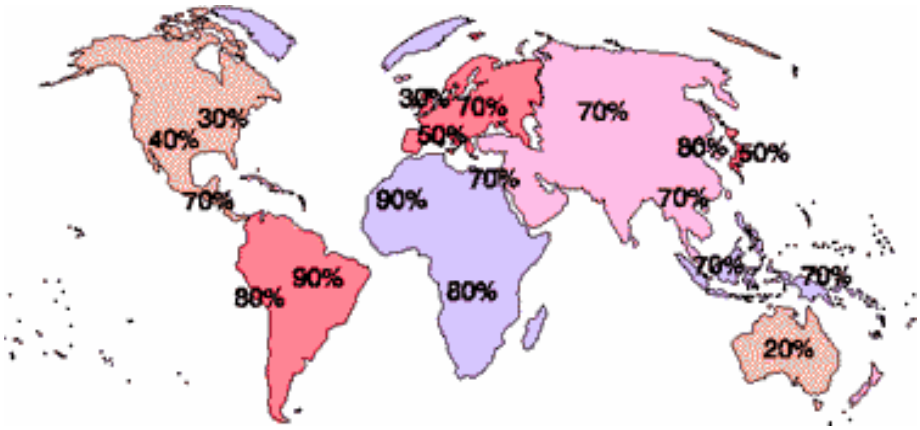

Figure (1): prevalence of H. pylori, Cited from www.medichems.com

Western Countries

- H.pylori affects about 20% of persons below the age of 40 years, and 50% of those above the age of 60 years.
- H.pylori is uncommon in young children.
- Low socio-economic status predicts H.pylori infection.
- Immigration is responsible for isolated areas of high prevalence in some Western countries. **(Rehnberg et al, 2001).**

Studies of sera from epidemiologists and Californians show that a 50% decline in the prevalence of H.pylori has occurred in the United States since 1968**. (Bazzoli et al, 2001)**.

Developing Countries

In developing countries most adults are infected. Acquisition occurs in about 10% of children per annum between the ages of 2 and 8 years so that most are infected by their teens. It is evident from careful surveys that the majority of persons in the world are infected with H.pylori. H.pylori can be cultured from the stools in most infected persons (using special techniques). This is evidence that spread by fecal oral contact with infected persons is likely. In addition, polymerase chain reaction (PCR) can detect H.pylori in dental plaque from 30% of persons with the gastric infection. This may be a less common source of transmission. **(Abasiyanik et al, 2000)**, **(Bazzoli et al , 2001)** , **(Fernando et al, 2001)** and **(Malaty et al , 2001).**

Factors associated with prevelance of H. pylori

- Socioeconomic status
- Age and race
- Sex
- Genetic
- Life style
- Environmental

Socioeconomic status

H. Pylori infection is inversely associated with socioeconomic status. The prevalence of H. pylori differs significantly both between and within countries, with high rates of infection being associated with low socioeconomic status and high densities of living **(Malcolm et al, 2004).**

Age and Race

The seroprevelance of H. pylori infection in a cohort of 99 black and 125 white US children was monitored over the period 1975/6 - 1995/6. H. pylori prevalence increased overall from 8% at 1-3 years, to 24% at 18-23 years .initially and throughout follow-up, a significantly higher prevalence of infection was observed in black as compared with white children, with the relative risk of sero-conversion being three times higher in black children. The highest sero-conversion rates (2.1% per year) occurred in children 4-5 years **(Malaty et al, 2002).**

Sex

Data from various studies suggested an increased prevalence of H. pylori infection in men compared with women but frequently did not reach statistical significance. The reason for the possible gender differences in H. pylori prevalence is unclear but may be related to that young boys having poorer hygine than younger girls (**Kikuchi and Dore, 2005).**

Genetics

May impact disease prevalence, however, as evidenced by H. pylori concordance being higher in monozygotic than di-zygotic twins **(Malaty and Graham, 1994).**

Life style

Drinking of Alcohol seemed to protect against active H. pylori infection. This protective effect was dose dependent and similar for beer and wine. Alcoholic beverages have many direct and indirect effects on the

gastric mucosa, on gastric emptying, and on gastric acid secretion,and these may affect the living conditions of H. pylori in the stomach. In particular, moderate alcohol consumption might invigorate mucosal defense by its effect on prostaglandins. Both beer and wine are potent stimulants of acids secretion and gastric release, and the wine has strong antibacterial activity. **(Brenner et al, 1997).**

In a study by **Konturek et al, 2003** smokers were likely to have H. pylori infection than non-smokers but when adjusted for confounding factors this association was only observed in these smoking >35 cigarette/ day. Smaller cross section surveys have reported an association between smoking and H. pylori prevalence but these may not have adequately controlled for confounding factors. Potentially relevant effects of smoking include an increase in acid and pepsin secretion and changes in gastric motility, prostaglandin synthesis, gastric mucosal blood flow, and mucus secretion.

The proportion of subjects infected with H. pylori was lower in those that drink coffee but this relationship was of borderline statistical significance (**Moayyedi et al, 2002)**.

Environmental

In the recent study from Japan, H. pylori- specific DNA was detected in water samples from the middle and downstream, but not from upstream researches of four rivers in Japan. H. pylori could not be cultured from any positive DNA samples. The prevalence of H. pylori stool antigen in children was 10% near the middle reaches, and 24% near the downstream reaches, but 0%in area distance from the river. Hence river water may be a source of H. pylori infections **(Fujimora, 2004).**