Study of Prevalence of Helicobacter Pylori Infection and its Impact on GIT Bleeding in Patients with Hemophilia and von Willibrand Disease

Thesis

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By

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Abstract

Background: Helicobacter pylori has been clearly recognized as an important cause of gastritis and cases of peptic ulcer. Because these episodes present a life-threatening complication in patients with bleeding disorders, we investigated the prevalence of H. pylori infection in patients with hemophilia A, B and von Willebrand disease and assessed the risk of gastrointestinal bleeding associated with this infection.

Methods: 40 male patients above 12 years with hemophilia A, B or von Willebrand disease and 20 controls were included.
Patients and control were divided into two groups according to occult blood test result; either negative or positive

Results: 70 % of patients were H. pylori positive, of whom 5 patients tested positive for occult blood, while 60 % of control subjects were H. pylori positive, of whom only one tested positive for occult blood meaning that the odds ratio for developing H. pylori related GI bleeding in patients with bleeding disorder is 2.3913, Confidence Interval: 0.2485 to 23.0104, Z statistic: 0.755, Significance level: P= 0.4504

Conclusion: Helicobacter pylori screening and eradication therapy would be needed in patients with hemophilia in endemic areas.

Keywords: Helicobacter pylori , Hemophilia , von Willibrand's Syndrome, upper gastrointestinal bleeding.

List of abbreviations

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AAV	Adeno-associated Virus
AIDS	Acquired Immune Deficiency Syndrome
AVWS	Acquired von Willibrand Syndrome
BU	Bethesda Unit
CDC	Center for Disease Control
CI	Confidence Interval
CJD	Creutzfeldt-Jakob Disease
Da	Dalton
DDAVP	1-desamino-8-D-arginine vasopressin
ELISA	Enzyme Linked Immunosorbant Assay
FVIII	Clotting Factor VIII
FVIIIa	Activated Factor VIII
FVIII:C	Factor VIII Concentration
FIX	Clotting Factor IX
FIXa	Activated Factor IX
FLrFVIII	Full-length rFVIII
FIT	Fecal Immunochemical Test
FOBT	Fecal Occult Blood Test
GC	Gastric Cancer
GNI	Gross National Income
GT	Guaiac Test
HA	Hemophilia A
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHD	Hereditary Hemorrhagic Diseases
HIV	Human Immunodeficiency Virus
HMW	High Molecular Weight
H. Pylori	Helicobacter pylori
HPSA	Helicobacter pylori Stool Antigen
ICH	Intra-cranial Hemorrhage
IDA	Iron Deficiency Anemia

List of abbreviations

ISPCR	Inverse-shifting PCR
ITT	Intention To Treat
IU	International Units
KDa	Kilo Dalton
MALT	Mucosa Associated Lymphoid Tissue
NAT	Nucleic Acid Test
NSAID	Non-steroidal anti-inflammatory drugs
NPV	Negative predictive value
OD	Optical Density
OR	Odds Ratio
pd-APCC	Plasma-derived Activated Prothrombin Complex Concentrates
PPV	Positive predictive value
PPIs	Proton Pump Inhibitors
PWH	Persons with Hemophilia
PY	Person Years
REC	Research Ethics Commitee
RIBA	Ristocetin-induced platelet aggregation
rFVIII	Recombinant Factor VIII
rFIX	Recombinant Factor IX
RUT	Rapid Urease Test
TSEs	Transmissible Spongiform Encephalopathies
UBT	Urease Breath Test
UGI	Upper Gastointestinal
VNTR	Variable number of tandem repeats
vWD	von Willibrand Disease
vWF	von Willibrand Factor
vWF:Ag	von Willebrand Factor Antigen
vWF:RCO	von Willebrand Ristocetin Cofactor
WFH	World Federation of Hemophilia

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Helicobacter pylori, previously named Campylobacter pyloridis, is a Gram-negative, microaerophilic bacterium found in the stomach. It was identified in 1982 by Barry Marshall and Robin Warren, However, over 80 percent of individuals harboring the bacterium are asymptomatic. More than 50% of the world's population harbor H. pylori in their upper gastrointestinal tract. Infection is more prevalent in developing countries, and incidence is decreasing in Western countries. **(Brown, 2000).**

Helicobacter pylori has been clearly recognized as the main cause of gastritis and most cases of peptic ulcer, and it has also been implicated in the pathogenesis of gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (MALT). **(Ernst and Gold, 2000)**. It has been hypothesized that the host immunologic response against H. pylori plays a main role in determining gastric mucosal injury through the release of cytokines and the action of auto-antibodies against H1/K1-adenosine triphosphatase of gastric epithelial cells. **(Giovanni et al. 2001).**

Infection with Helicobacter pylori is the main etiological factor for erosive gastritis and duodenal or gastric peptic ulcers often complicated with life-threatening bleeding in patients with coagulation disorders **(Szczepanik et al., 2005).**

Many episodes of bleeding in the upper gastrointestinal tract are caused by Helicobacter pylori infection. Because these episodes present a life-threatening complication in patients with bleeding disorders, we prospectively investigated the prevalence of H. pylori infection in patients with hemophilia A or B or von Willebrand syndrome**.**

The aim of this prospective study is to evaluate the prevalence of Helicobacter pylori infection in hemophilic patients, and to assess its impact on gastrointestinal bleeding associated with this infection in such patients.

Chapter I

Helicobacter pylori

Helicobacter pylori (H. pylori) is perhaps one of the most common human infectious agents worldwide. Genetic sequence analysis has indicated that human being has co-evolved with H. pylori for more than 58,000 years. Since its discovery in 1982, H. pylori has been closely linked to a diverse spectrum of gastrointestinal diseases. At present, H. pylori is considered the most common etiologic agent for infection-related cancers, which represent 5.5% of the global cancer burden. **(Wang et al., 2014).**

Helicobacter pylori is a small, curved, highly motile, Gram negative bacillus that colonizes only the mucus layer of the human stomach. **(Logan and Walker, 2001).**

It was first isolated by Warren and Marshall in 1983 (Fig. 1). It induces chronic inflammation of the underlying mucosa (Fig. 2). The infection is usually contracted in the first few years of life and tends to persist indefinitely unless treated. Its prevalence increases with older age and with lower socioeconomic status during childhood and thus varies markedly around the world. The organism can survive in the acidic environment of the stomach partly owing to its remarkably high urease activity; urease converts the urea present in gastric juice to alkaline ammonia and carbon dioxide **(McColl K., 2010).**

Figure 1. Helicobacter pylori.
H. pylori is a gram-negative bacterium with a helical rod shape. It has prominent flagellae, facilitating its penetration of the thick mucous layer in the stomach.
(McColl K., 2010)

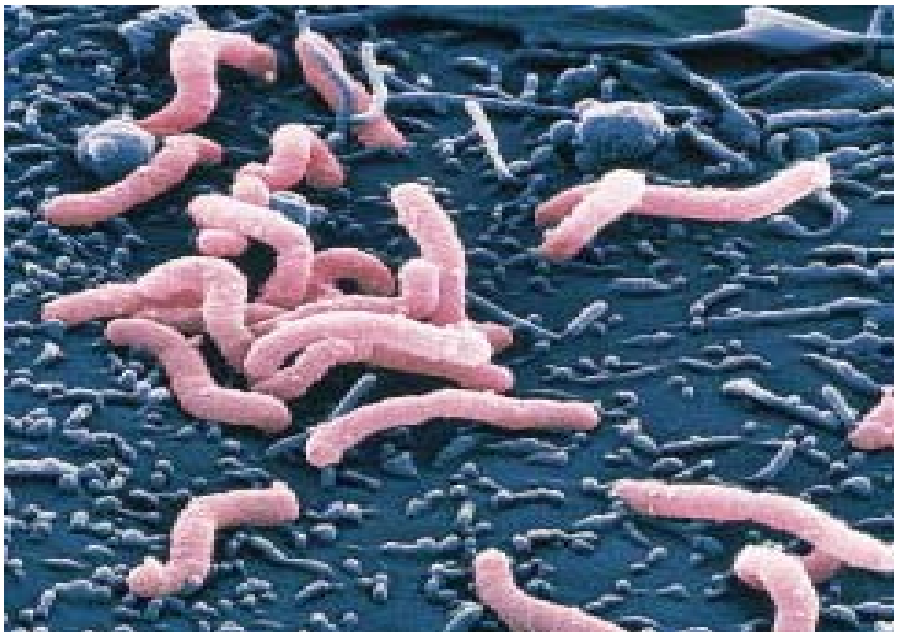


Figure 2

Colored scanning electron micrograph of H pylori on surface of gastric cell **(Logan and Walker 2001)**

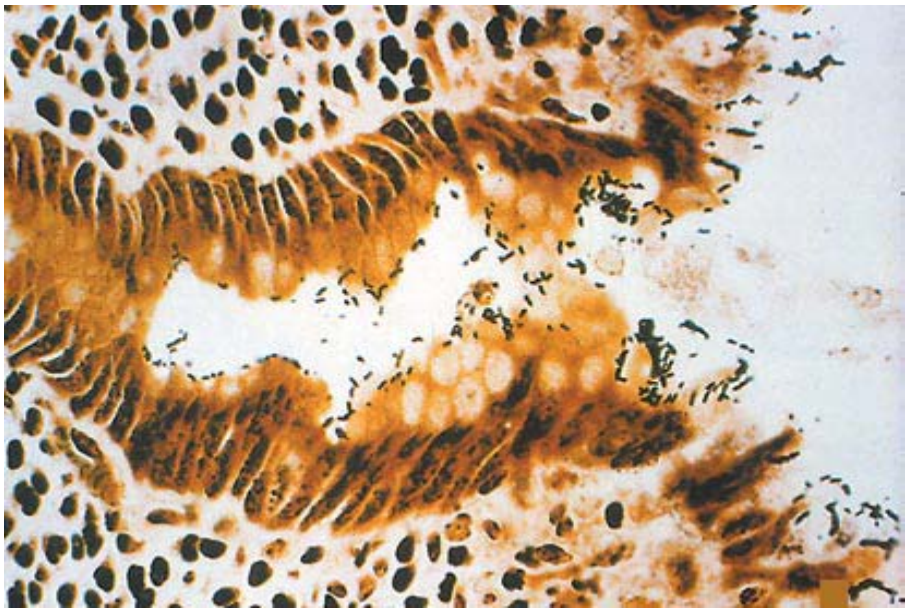


Figure 3

Gastric-biopsy specimen (by electron microscope) showing Helicobacter pylori adhering to gastric epithelium and underlying inflammation. H. pylori is visible as small black rods on the epithelial surface and within the glands. The underlying mucosa shows inflammatory-cell infiltrates. **(McColl K., 2010)**

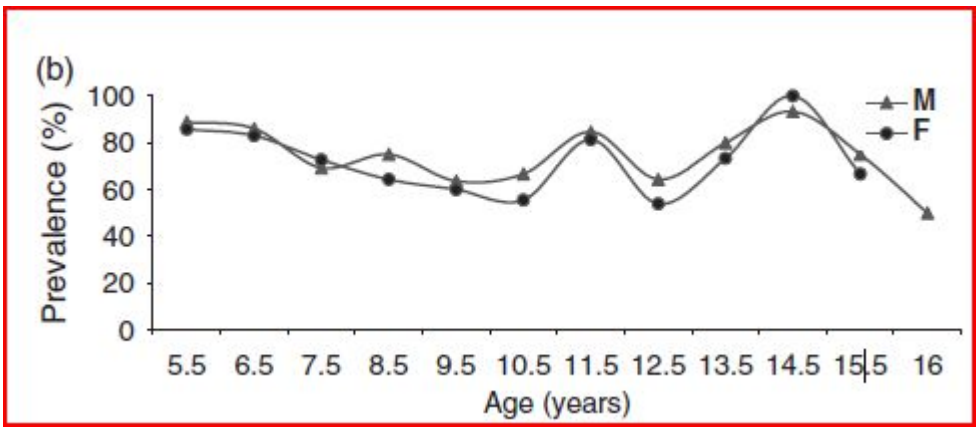
- **Epidemiology**

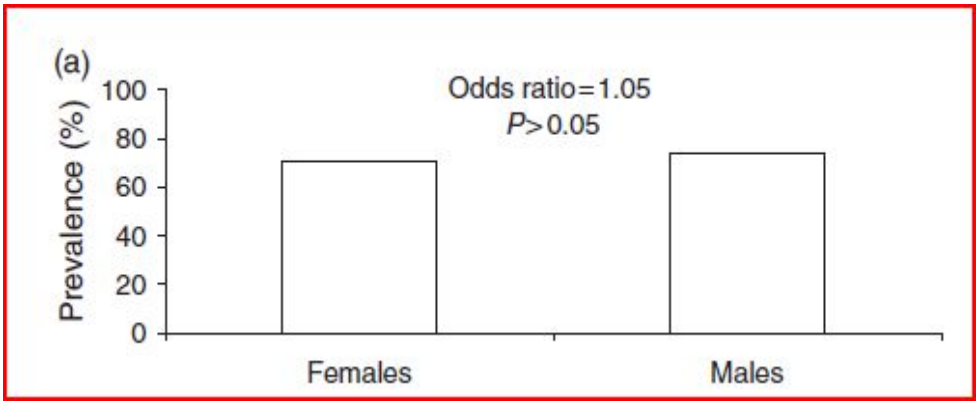
In 1995 Pounder and Ng classified the world into two groups according to the incidence of H. pylori infection. Group one consisted of countries where the majority of children become infected with H. pylori during childhood, while chronic infection continues during adult life. These are mostly developing countries, e.g., Algeria, Nepal, South Africa, Saudi Arabia, Thailand, and Vietnam. In Group Two, mostly comprising developed countries, only a minority of children becomes infected during childhood, but the prevalence of infection rises with age during adulthood. Examples of Group two countries are England, Finland, France, Japan, and the United States of America**. (Pounder and Ng., 1995**).

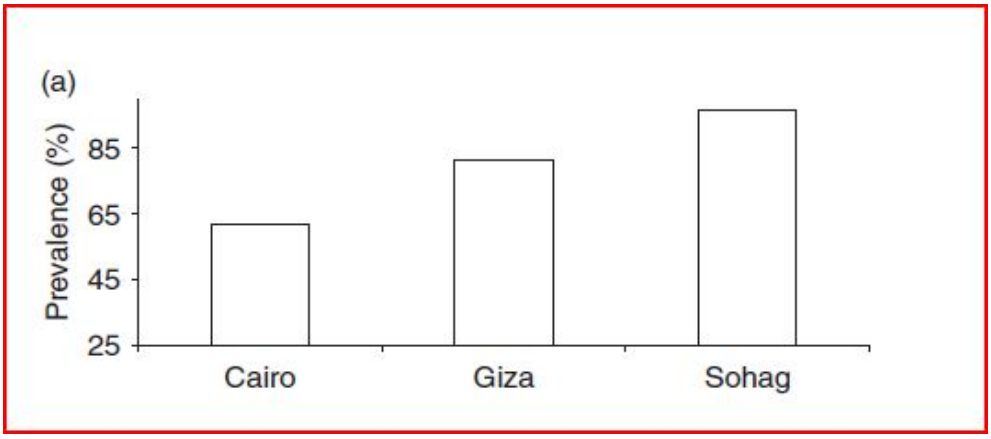
- **Prevalence in Egypt**

The prevalence of H. pylori varies with the geographic regions, age, socio-economic status, education level, living environment and occupation. The vast majority of H. pylori infection occurs in the developing countries where up to 80% of the middle-aged adults may be infected. In contrast, the world's average prevalence of H. pylori infection was reported to be 58%. **(Wang et al., 2014).**

A cross-sectional population-based study was conducted in Egypt among 286 school children (168 boys and 118 girls), with a mean age of 11.04 years, to determine the prevalence of H. pylori. The presence of the bacterium was assessed using the [^{13}C]urea breath test. The parents of the children enrolled in the study responded to a structured questionnaire with the help of school teachers to obtain parental data on occupation, education level and environmental information, such as the number of persons living in the house, type of house, number of rooms in the house, availability of potable water and sanitary conditions. Education and occupational levels of both parents were recorded and used to define the index of socio-economic class. A score of 1 was given to children whose school was in a deprived area, score 2 for children with more than three persons per room at home, and score 3 for children whose fathers were university graduates and were attending school in a high-class area. Height and weight were analyzed in relation to H. pylori infection resulting with overall prevalence of H. pylori infection was 72.38%. Attending school in a socially deprived area and residing in an overcrowded home were the major risk factors for infection. Differences between infected and non-infected children were significant with regard to body weight and height (weight p= 0.05; height: p= 0.009). The number of children (both boys and girls) falling below the 5th percentile of height-for-age was significantly higher in infected than non-infected children (p= 0.001). **(Mohammad et al., 2007)**.







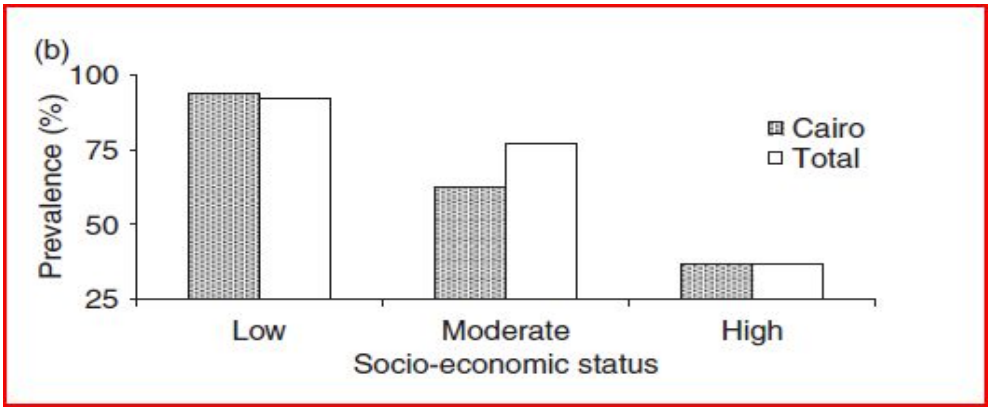


Figure 4 Prevalence of h pylori in different age, sex, residence area and socio economic status. **(Mohammad et al., 2007)**.

These results are similar to the study published in The Journal of the Egyptian Public Health Association in 2001 indicating crowdedness as risk factor as the prevalence among children where ≥ 3 share a bed was 59.7% compared to only 26.9% among those where < 3 persons share a bed **(Omar et al., 2001).**

A seroprevalence rate of 75.5%. H. pylori exposure was higher in adults (79.33%) than in children (64%) and it was statistically significant. The seroprevalence of infection was higher in rural areas (87.3%) than in urban areas (40%). **(Sayed et al., 2007)**

- **Mode of transmission**

Although how H. pylori is acquired is usually unknown **(Logan and Walker, 2001)**. It is transmitted largely by the oral–oral or fecal–oral. World Gastroenterology Organization identified factors that play role in transmission of H pylori; lack of proper sanitation, of safe drinking water, and of basic hygiene, as well as poor diets and overcrowding. **(Hunt et al., 2011)**.

A recent Egyptian study suggested contaminated water as one of the likely candidate sources of transmission of H. pylori. **(Aziz et al., 2013).**

- **Effect on infected patients**

Although the majority of individuals infected with H. pylori remain asymptomatic throughout their life, essentially all develop chronic inflammation. Among infected individuals, approximately 10% develops peptic ulcer disease, 1–3% progresses to gastric cancer (GC), and 0.1% develops mucosa-associated lymphoid tissue (MALT) lymphoma. Of the various diseases that are closely associated with H. pylori infection, gastrointestinal malignancies are perhaps the most important entities requiring extensive studies. **(Wang et al., 2014).**

The World Health Organization has categorized H. pylori as a class I carcinogen **(Goto et al., 1999)**, and direct evidence of carcinogenesis has been demonstrated in animal models **(Honda et al., 1998)**. Searching for and eradicating H pylori can reduce the incidence of gastric cancer in healthy asymptomatic infected individuals. **(Ford et al., 2014).**