

Research Article

Association of *cag E Gene* and LL-37 Serum Level with *Helicobacter pylori*-induced Peptic Ulceration in Egyptian Patients

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Abstract

Background and aim: Variation in the clinical outcome of *Helicobacter pylori (H. pylori)* induced pathology is multifactorial, involving a complex interplay between the host immune responses and pathogen virulence factors.

Patients and methods: This study included 95 *H. pylori* infected patients who underwent endoscopy. They selected if culture and/or histopathological examination and rapid urease test were positive. All patients were examined for presence of *cag E* and LL-37.

Results: Endoscopic findings in the patients were variable. The most frequent findings was gastritis 45.3% (43/95), followed by duodenitis; 36.8% (35/95), duodenal ulcer; 14.7% (14/95), esophagitis; 11.6% (11/95) and the least frequent one was gastric ulcer; 4.2% (4/95). Interestingly, *cag E* was positive in 27.4% of patients (26/95). As regards LL-37, its mean \pm SD was 123.25 ± 20.26 ng/mL. Classifying studied patients into peptic ulcer and non peptic ulcer groups, *cag E* was positive in patients with peptic ulcer more than those who were non peptic (88.9 % versus 13%) (OR=0.019; CI 0.004-0.094) and P<0.001. The difference between two groups as regard LL-37 was statistically significant (CI 44.87-51.98), P<0.001.

Conclusion: This study concluded that there was a strong association of *cag E* and LL-37 serum level with *H. pylori*-induced peptic ulceration in Egyptian patients.

Keywords: *Cag E* gene; LL-37 Serum level; *Helicobacter pylori*; Peptic ulceration; Egyptian patients

Introduction

Helicobacter pylori (H. pylori) is a gram negative, non-spore forming spiral bacterium which colonizes the human stomach [1]. H. pylori is prevalent worldwide; nearly 50% of the population is infected with H. pylori. The prevalence, incidence, age distribution and sequels of infection are significantly different in developed and developing countries [2]. One Egyptian study in rural area found the overall seropositivity rate of 91.7% when screened for anti-H. pylori antibodies among six hundred and five people [3]. Individuals infected with H. pylori have a 10 to 20% lifetime risk of developing peptic ulcers and a 1 to 2% risk of acquiring stomach cancer [4,5] and type B low-grade mucosal-associated lymphoma [6]. Furthermore, the organism is also thought to be involved in other human illnesses such as hematologic and autoimmune disorders, insulin resistance and the metabolic syndrome [7-9].

Variation in the clinical outcome of *H. pylori* induced pathology is multifactorial, involving a complex interplay between the host immune responses and pathogen virulence factors. Several putative genes, such as cytotoxin associated gene (*Cag*)*A*, *CagE*, vacuolating cytotoxin A (*vacA*), induced by contact with epithelium (*iceA*) and blood-group antigen-binding adhesion (*babA2*), have been identified and are likely to play an important role in the pathogenicity of the bacterium [10-12]. *Cag E* is shown to increase secretion of chemokines, such as interleukin (IL)-8, from infected host epithelial cells [13-15]. IL-8 is a potent neutrophil chemoattractant and so could mediate the initial host inflammatory response to *H. pylori* infection, present in infected gastric mucosa [16].

As regards host immune factors against H. pylori infections, the innate production of proteins and peptides with antimicrobial activity by gastric epithelial cells provides a layer of host innate defense [17,18]. Cathelicidins; a family of host defense peptides are naturally expressed by cells of the gastrointestinal tract (GIT). The single known cathelicidin in man is human cationic antibacterial protein of 18 kDa (hCAP18), whose C-terminal 37 amino acid peptide is termed LL-37. LL-37 is proteolytically cleaved to be released as a functional antimicrobial peptide. LL-37/hCAP18 has a distinct distribution in the intestinal tract, with its expression being greatest in the surface and upper crypt epithelium in the colon and sparse to absent in small intestinal epithelium, with the exception of Brunner's glands in duodenum [19]. In normal stomach, the expression of LL-37/hCAP18 is restricted to differentiated surface of various types of cells including epithelial cells, chief cells and parietal cells and is also present in the stomach secretion. It is upregulated during infection, inflammation and wound healing both in animals and humans [19-22]. The increasing level of LL-37 may help fighting bacterial infection at the early stage. However, during the

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progression from atrophic gastritis to adenocarcinoma, the expression of LL-37 is reduced [22].

On the other hand, the expression of LL-37 is low or absent in chronic ulcers, as when antibodies to this peptide was administrated, it may inhibit post wounding re-epithelialization [23].

This study aimed to detect whether there is an association of *Cag E* and LL-37 serum level with *H. pylori*-induced peptic ulceration in Egyptian patients.

Patients and Methods

Research design

This Cross sectional study was conducted at Internal medicine, Clinical Pathology and Medical Microbiology and Immunology Departments, Faculty of Medicine, Zagazig University, Egypt during the period from April 2014 to June 2015. This study included 95 *H. pylori* infected patients. They were 64 males and 31 females and their ages were 32-55 years old. All patients underwent full history taking including dyspeptic symptoms; that includes epigastric pain, bloating, nausea, vomiting, early satiety and hematemesis and melena. Routine laboratory tests including urine and stool analysis, complete blood picture, *erythrocyte sedimentation rate* (ESR), liver and kidney function tests were done. Abdominal ultrasonography was also done to exclude any abdominal mass (inflammatory or cancers).

Exclusion criteria

Patients were excluded if they had recently (within the last 15 days) received antibiotics or had been treated for *H. pylori* in the last seven days, they use drugs as aspirin or NSAIDs which is a confounding variable in the development of gastritis and ulcer.. Also, excluded cases of any bacterial infection induced inflammation or GIT cancers.

Ethical considerations

This study was approved by medical ethical committee of Faculty of Medicine, Zagazig University. A written informed consent was obtained from all the patients.

Diagnosis of the H. pylori infection

All subjects were underwent endoscopy after overnight fasting using endoscope (GIF XQ230; Olympus, Center Valley, PA) for evaluation of dyspepsia and infection with H. pylori. Two biopsies were obtained; an antral biopsy about 2 cm of the pylorus and another from the corpus of the stomach for bacterial isolation [24]. For cultures to detect H. pylori, the specimens were transported to the laboratory in 0.2 mL of 20% glucose broth (BioMerieux) in sterile screw-capped tubes at 4°C within two hours. Before culture, the specimens were grounded and homogenized with a sterile mortar and pestle in 1 mL of saline. The biopsy homogenate was placed onto a Columbia blood agar plate with antibiotics supplement set; trimethoprim, vancomycin, and amphotericin B. The plates were incubated under microaerophilic conditions; 5% O_2 , 7.5% CO_2 , 7.5% H_2 , and 80% N_2 using Campy Pak microaerophilic system envelopes (Columbia Diagnostics, Springfield, VA) at 37°C for up to ten days. The plates were checked every other day for growth. On day 5, the plates without obvious growth were subcultured onto Columbia blood agar plates to promote growth of lightly growing colonies that may have been missed visually. All colonies that were small, circular, and smooth colonies suggestive of H. pylori were tested with Gram-stain, oxidase, catalase, and urease tests to confirm the identification [25].

The *H. pylori* infection was considered positive if the culture and/or histopathological examination and rapid urease test were positive [26]. All the isolated *H. pylori* were suspended in 2 mL of tryptone soy broth medium containing 20% (vol/vol) glycerol and kept frozen at -70°C until DNA extraction was performed [27].

Detection of pathogenicity gene CagE by PCR:

Extraction of genomic DNA

Chromosomal DNA was extracted from *H. pylori* isolates using a commercially available kit (QIAGEN Inc., Valencia, CA, USA) according to the manufacturer's guidelines.

Genotyping of the CagE gene

It was performed as described by Ikenoue et al. [28]. The distal regulatory region was amplified using the following primers that obtained from (Biolegio, Netherlands):

CagE-F1 5'-GCGATTGTTATTGTGCTTGTAG-3' and *CagE*-R1 5'-GAAGTGGTTAAAAAATCAATGCCCC-3'. Each PCR of *Cag E* was performed in a total volume of 50 μ l containing 100 ng genomic DNA from *H. pylori* culture, 200 μ M each of dNTP, 1X PCRbuffer (20 mMTris-HCl, pH 8.4), 50 mMKCl, 1.5 mM MgCl₂, 0.5 μ M of each primer, and 1.5 units of Taq polymerase. Negative controls were added to each PCR run including all reagents except template DNA which was substituted with ultrapure water. PCR was performed in a heated lid thermal cycler)Biometra, Germany). PCR amplification conditions were optimized as follows: initial denaturation for 5 min at 94°C was followed by 40 cycles of denaturation at 90°C for 30 s, annealing at 52°C for 30 s, and extension at 70°C for 1 min and a final extension at 70°C for 10 min.

Aliquots of amplified samples (10 μ l) were electrophoresed on 2% agarose gel in 1X TAE buffer (40 mMTris-acetate, 1 mM EDTA [pH 8.0]) containing ethidium bromide (0.5 μ g/ml), and then the amplified bands (329 bp) were visualized under a UV transilluminator) Biometra, Germany).

Determination of Cathelicidin LL-37 serum level

It was measured by performing an enzyme-linked immunosorbent assay (ELISA) with commercially available kit (HK 321 Humman LL37 Elisa Kit, Hycult biotechnology, Uden. Netherlands). The minimum detectable concentration of serum LL-37 when using this assay was 0.1 ng/mL.

Statistical analysis

All patients' data were tabulated, and then processed using Statistical Package for Sciences and Society SPSS (version-11). Odds ratios (OR) 95% confidence intervals (CI) was calculated to assess the relative difference between non peptic ulcer and peptic ulcer groups (as regards *Cag E*) in *H. pylori* infected patients. The t-test was used to evaluate the age and LL-37 differences between the two groups. Also, 95% confidence intervals (CI) was done regarding LL-37. Chi square and P value were used to calculate sex, *Cag E* genotype frequency differences in the two groups (sex, *Cag E*). P value less than 0.05 were regarded as significant.

Results

This current study assessed whether *Cag E* and LL-37 serum level affected the outcome of *H. pylori* infection. The descriptive data of the patients were analyzed and presented in Table 1. The study included 64 (67.5%) male and 31 (32.5%) female. Dyspeptic symptoms were

	N=95	%			
Sex					
Male	64	67.5%			
Female	31	32.5%			
Symptoms					
Nausea	72	75.8%			
Vomiting	70	73.7%			
Bloating	60	63.1%			
Early satiety	44	46.3%			
Epigastric pain	35	36.8%			
Hematemesis and melena	3	3.1%			
Endoscopic findings					
Gastritis	43	45.3%			
Duodenitis	35	36.8%			
Duodenal ulcer	14	14.7%			
Esophagitis	11	11.6%			
Gastric ulcer	4	4.2%			
Cag E					
Present (+)	26	27.4%			
Absent (-)	69	72.6%			
LL-37 serum level (ng/mL)					
Mean ± SD	123.25 ± 20.26				

 Table 1: Descriptive data (demographic, clinical, endoscopic findings, cag E and LL-37 serum level) of studied patients.

	Non peptic ulcer group N=77	Peptic ulcer group N=18	OR (95%CI)	Р	
Age (32-55)	42.5 ± 6.98	41 ± 7.5	-	0.427	
Sex					
Male (n= 64)	52(67.5%)	12(66.7%)	-	0.575	
Female (n= 31)	25 (32.5%)	6 (33.3%)			
Cag E					
Present (+)	10(13%)	16 (88.9%)	0 .019 (0.004- 0.094)	<0.001	
Absent (-)	67(87%)	2 (11.1%)			
LL-37 serum level (ng/mL)					
Mean ± SD	84 ± 5.8	132.43 ± 7.5	(44.87-51.98)	<0.001	

 Table 2: Differences between non peptic ulcer and peptic ulcer *H. pylori* patients groups as regards age, sex, cag E and LL-37 serum level.

variable where most frequent symptom was nausea (n=72, 75.8%), followed by vomiting (n=70,73.7%), bloating (n=60, 63.1%), early satiety (n=44, 46.3%) and epigastric pain (n=35, 36.8%) and the least frequent symptom was hematemesis and melena in about 3 patients only (3.1%). As regards endoscopic findings, gastritis was the most frequent finding; 45.3% (43/95), followed by duodenitis; 36.8% (35/95), duodenal ulcer; 14.7% (14/95) and esophagitis; 11.6% (11/95) and the least frequent finding was gastric ulcer 4.2% (4/95). Interestingly, *Cag E* was positive in 27.4% of patients (26/95). As regards LL-37, its mean \pm SD was 123.25 \pm 20.26 ng/mL. Table 2 shows that there was no statistically significant differences between non peptic ulcer and peptic ulcer groups as regards age and sex. *Cag E* was positive in patients with peptic ulcer more than those who were non peptic (88.9 % versus 13%) (OR=0.019; CI 0.004-0.094) and P<0.001. Moreover, the difference between the two groups as regard LL-37 was statistically significant (CI 44.87-51.98), P<0.001.

Discussion

Helicobacter pylori, a bacterium adapted to colonize the gastric mucosa, is considered to be the main etiological agent of gastritis and also a risk factor for peptic ulcer and gastric cancer in humans [29,30]. Factors related to the host, the diversity of bacterial pathogenicity and the

environment seem to be related to the broad clinical spectrum related to infection by H. pylori [31]. Cag E gene is one of virulence factor in the H. pylori organism affecting its pathogenesis potential effect in the gastric mucosa [32]. On the other hand, H. pylori upregulates LL-37/hCAP18 production by the gastric epithelium, suggesting that cathelicidin or its derivative LL-37 contributes to combat chronic infection with this gastric pathogen [22,33]. In this research, there was overlap between dyspeptic symptoms in studied patients. This work reported that most frequent endoscopic finding was gastritis 45.3% (43/95), followed by duodenitis; 36.8% (35/95), duodenal ulcer; 14.7% (14/95) and esophagitis; 11.6% (11/95) and the least frequent finding was gastric ulcer 4.2% (4/95). In disagreement with our findings, another research in Kuwait, reported that 57.6% (57/99) of patients had gastritis, 61.6% (61/99) had duodenal ulcer and 1% (1/99) had gastric ulcer [34]. The more aggressive endoscopic findings in studied patients in Kuwait more than Egypt may be due to host genetic or environmental difference between the two countries. As regards age and sex between non peptic ulcer and peptic ulcer groups, our results found no significance results.

Page 3 of 9

The current study confirmed the role of Cag E as an important virulent factor related to H. pylori pathogenicity as we detected significance difference between the two groups regarding its prescence (P<0.001). This was in concordance with other studies that showed the presence of Cag E-positive isolates were associated with duodenal ulceration. For instance, in a study by Fallone et al. [35], 31 (37%) out of 84 patients with gastroduodenal disease (including both peptic ulceration and gastric cancer) were infected with Cag E-positive strains, compared with only 20.7% of 92 patients with gastritis alone (P=0.02). Also, our results matched with that of Ramis et al. [33] as they detected that Cag E is a biomarker for gastric lesions and increasing pathogenic potential of H. pylori infection. In addition, Day et al. [36] detected that 12 out of 13 children (92%) with duodenal ulcers were infected with Cag E-positive isolates, compared with only 5 out of 16 (31%) with gastritis alone. Although French study found that 51 out of 56 (91%) strains isolated from patients with duodenal ulcers were Cag E-positive, whereas 13 out of 17 (76%) H. pylori isolates obtained from patients with gastritis alone were positive but with non statistically significant difference between duodenal ulcer and gastritis patents [37]. This difference was explained as different geographic location of the patients may affect the results of the studies. It is clear that Helicobacter isolates in humans from different regions of the world are variable [38,39].

Regarding LL-37, our study found significant increase in LL-37 serum level in peptic ulcer group more than non peptic ulcer group. This in accordance with another study that estimated the level of LL-37 in gastric secretion. In addition, many previous studies interested in role of LL-37 in promotion of mucosal repair in GIT [40], mentioned that, during inflammation, LL-37 decrease pathogenic microbes, inflammatory cytokines and apoptosis, increase mucus secretion by activation of MAP kinase, formyl peptide receptor and mucin genes with electrostatic interaction on microbial membrane [41-44]. On the other hand, in presence of ulceration, it leads to increase cell proliferation, re-epithelialization and angiogenesis by activation of growth factors and their receptors [21,45,46].

As *Cag E* and LL-37 have a significant role in pathogenic progress of *H. pylori* infection, dealing in the future with these results may help to treat *H. pylori* and stopping its pathogenic progress. Also, supplementation with this host defense peptide as LL-37 orally seems to be a promising approach to treat different disorders in the GIT.

Conclusion

This study concluded that there is high impact of *Cag E* and serum LL-37 on pathogenicity and severity of *H. pylori* infection in Egyptians.

Recommendation

We recommended other studies that deal with other factors affecting the aggressive attitude of *H. pylori* infection and other trials to use new strategy in treatment of this infection.

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Page 4 of 9

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Page 5 of 9

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