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Role of *Helicobacter pylori* infection in etiology of systemic lupus erythematosus

Ali Hafedh Abbas[1,2]*, Alice Krekor Melconian[2] and Ali Hussein Ad'hiah[1]

[1] *Tropical-Biological Research Unit, College of Science, University of Baghdad, Iraq.*
[2] *Biotechnology Department, College of Science, University of Baghdad, Iraq*.

* Corresponding author: Ali Hafedh Abbas; e-mail: ali_habbas@scbaghdad.edu.iq

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disorder, caused by a production of autoantibodies against self-antigens before the appearance of clinical symptoms. The disease etiology is unknown, although there are several infectious agents that have been suggested to be involved in the induction of SLE, especially in genetically predisposed individuals. One of these agents is *Helicobacter pylori*, and accordingly, the current study assessed anti-*Helicobacter pylori* IgG antibody by enzyme linked immunosorbent assay in sera of 64 SLE female patients and 32 health control women. The patients were distributed into two equal groups (32 cases in each group); the first involved patients with renal complications (nephritis), while the second group included patients that have arthritis. In both groups of SLE, a significant ($p \leq 0.001$) increased percentage of sero-positive cases for anti-*H. pylori* IgG antibody was observed (62.5 and 31.3%, respectively) compared to control group, in which all women were sero-negative. These results may propose that *H. pylori* infection is one of the etiological factors involved in etiopathogenesis of SLE.

Keywords: Anti-*Helicobacter pylori* IgG antibody, Infectious agents, Systemic lupus erythematosus.

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease, in which a genetic effectiveness plays an eminent role in determining the disease incidence; however, an absence of tolerance for self-nuclear antigens is considered to play a pivotal role in the disease manifestation [1, 2]. It has been reported that 40% of SLE patients are defective in clearance of apoptotic cells, which are normally removed rapidly by phagocytes in healthy individuals [3].

As aforementioned, the etiology of SLE is imposed by a genetic background, but environmental factors are required to trigger the disease in genetically predisposed individuals; especially in females, in which sex hormones strongly influence the disease pathogenesis [4, 5]. This may lead to an irreversible break in immunological tolerance manifested by an immune response against endogenous nuclear antigens [6].

The concept of relationship between environmental factors and autoimmunity has been significantly increased during the last years. Among the environmental factors that have been suggested to have a role in etiology of SLE are different infectious agents; for instance, viral infections (Epstein-Barr virus; EBV, retroviruses, paramyxovirus, cytomegalovirus; CMV, parvovirus B19 and coronavirus) [7, 8, 9]. In addition, bacterial infections (*Chlamydia trachomatis*, *Mycobacterium tuberculosis*, *Helicobacter pylori*, *Escherichia coli*, *Streptococcus pneumoniae*, *S.pyogenes*, *Proteus mirabilis*, *Chlamydia pneumonia* and *Mycoplasma pneumonia*) have also been suggested [10-14]. Molecular mimicry is one of the proposed theories that explain the role of these agents in triggering SLE. A bacterial cell wall or flagellar components that share amino acid sequences with self-amino acid sequences of host may initiate cross-reactive T- and B-cell responses [15]. In this situation, autoreactive T-cells

with T-cell receptors that recognize both a foreign peptide (bacterial peptide) and a self-peptide (host peptide) have been delineated [7, 16].

H. pylori is a widespread gram-negative bacterium, which infects the gastrointestinal mucosal membrane, and since its early discovery as a human pathogen in 1984 by Marshal and Warren, a relationship with numerous diseases have been reported [17]. The presence of *H. pylori* in the gastric mucosa can lead to many complications; for instance, peptic ulcer, non-cardia gastric adenocarcinoma, and gastric mucosa associated lymphoid tissue (MALT) lymphoma [18]. Human becomes infected with this bacterium through direct contact with body fluids (saliva, vomit or fecal matter, and also fulminate through the contaminated food or drink) that have the bacteria [19]. Epidemiological studies have demonstrated that *H. pylori* infection plays a pivot role in etiopathogenesis of inflammatory and proliferative diseases; for instance, rheumatoid arthritis, SLE, Sjögren's syndrome, systemic sclerosis, autoimmune thyroid disease, multiple sclerosis, neuromylitis optica and cancer [20].

Accordingly, the current investigation aimed to determine anti-*H. pylori* IgG antibodies in sera of Iraqi SLE female patients. Two clinical complications of the disease were also considered; nephritis and arthritis.

2. MATERIALS AND METHODS

The study was approved by the ethical committee of Iraqi Ministry of Health, in which 64 SLE female patients were enrolled. Their age range was 23 - 36 years (32.5 ± 1.1 years). They were referred to the Consultant Clinic at the Department of Rheumatology (Baghdad Teaching Hospital) during the period January – March 2016 for diagnosis and treatment. The diagnosis was made by the consultant medical staff at the clinic according to the 1997 revised criteria for SLE of the American College of Rheumatology (ACR). They are based on a clinical examination and a laboratory evaluation [21]. As suggested by the consultants, the patients were distributed into two clinical groups that were nephritis and arthritis; each of 32 patients. In addition to patients, 32 apparently healthy women were also enrolled in the study (control group); matched patients for age (33.1 ± 1.4 years).

Sera of patients were first tested for anti-nuclear antibodies (ANA), which were detected by ANA-LIA MAXX kit (Human Company, Germany). After that, anti-*H. pylori* IgG antibody was assessed by using a commercially available kit (DEMEDITEC Company, Germany). The kit is based on the principles of ELISA. The microtiter strip wells (solid phase) are coated with *H. pylori* antigens that allow the detection of anti-*H. pylori* IgG antibodies in human sera.

The data are given as numbers and percentage frequencies, and significant differences between these frequencies were assessed by two-tailed Fisher's exact probability. In addition, odds ratio (OR) and etiological fraction (EF) were also estimated. These statistical evaluations were carried out by using WIN PEPI software version 11.61.

3. RESULTS AND DISCUSSION

The sera of both groups of SLE patients were positive for ANA (100.0%), while none of the control sera was positive for these autoantibodies; therefore, the diagnosis of SLE was ascertained, because most investigators agree that sera of SLE patients show a positive reaction for ANA [21, 22].

With respect to anti-*H. pylori* IgG antibody, 62.5% of nephritis patients were positive for anti-*H. pylori* IgG antibody; while such antibody was not detected in controls. Such difference was significant ($p = 7.1 \times 10^{-6}$), and associated with OR of 57.57. In addition, the differences scored EF of 0.46, (Table 1). Such profile was almost similarly observed in arthritis SLE patients, with the exception that a lower OR value was recorded (30.33) (Table 2).

Table 1: Observed numbers and percentage frequencies of positive sera for anti-*H. pylori* IgG antibody in nephritis systemic lupus erythematosus patients and controls.

Anti- *H. pylori* IgG antibody	Nephritis Patients (No. = 32)		Controls (No. = 32)		Odds Ratio	Etiological Fraction	*p*	95% Confidence Interval
	No.	%	No.	%				
Positive	20	62.5	0	0.0	57.57	0.46	7.1×10^{-6}	3.4 - 977.1
Negative	12	37.5	32	100.0				

p: Two-tailed Fisher's exact probability

Table 2: Observed numbers and percentage frequencies of positive sera for anti- *H. pylori* IgG antibody in arthritis systemic lupus erythematosus patients and controls.

Anti- *H. pylori* IgG antibody	Arthritis Patients (No. = 32)		Controls (No. = 32)		Odds Ratio	Etiological Fraction	*p*	95% Confidence Interval
	No.	%	No.	%				
Positive	10	31.3	0	0.0	30.33	0.31	8.5×10^{-4}	1.8 - 520.9
Negative	22	68.7	32	100.0				

p: Two-tailed Fisher's exact probability

The presented findings suggest that anti-*H. pylori* IgG antibody might be involved in the etiopathogenesis of nephritis and arthritis in SLE patients, especially if we consider the OR value that had a range of 30.3 –57.5. In statistical interpretation, individuals' positive for this antibody is at greater risk to develop SLE compared to individuals negative for this antibody; therefore *H. pylori* infection might be considered as one of the infectious agents involved in etiology of SLE. Many research groups have focused on the role of *H. pylori* infection in the etiopathogenesis of SLE, and their results reported that *H. pylori* might be involved in inducing clinical symptoms mimicking lupus flares in SLE patients [23, 24, 25]. In addition, the severity of clinical features was found to be considerably higher in patients with positive anti- *H. pylori* IgG than in SLE patients with negative anti- *H. pylori* IgG [24].

However, in further studies, the subject of *H. pylori* infection in SLE was deeply investigated. [26] and [27] analyzed the relevance of human *H. pylori* infection in SLE patients by analyzing serum samples of patients. Their data indicated that the frequency of positive anti-*H. pylori* IgG antibody showed no significant different between SLE patients and controls, but the titers of anti-*H. pylori* IgG antibodies in SLE patients were significantly higher than that of controls. [28] and [29] disagreed with this finding; they reported that *H. pylori* has a protective role against SLE development. Together, these data (including the data of present study) are in favor with that of *H. pylori* is associated with an increased risk to develop SLE in infected patients.

4. CONCLUSION

The present findings suggest that *H. pylori* infections might be involved in the etiopathogenesis of nephritis and arthritis in SLE patients, and considered as one of the infectious agents involved in etiology of SLE.

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Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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