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The Lapin Immune States Associated with Intravenous Injection of Heat Killed Antigen Extracted from Helicobacter *pylori* Infection in Hilla City

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Abstract
Helicobacter pylori is considered to be the most common human bacteria in the pathogenesis of chronic gastritis and peptic ulcer diseases. gastric inflammation associated with the infiltration of various immune cells into the infected gastric mucosa . The immune and inflammatory response is ineffective, allowing lifelong bacterial persistence, the host immune response is unable to clear the infection and may actually contribute to the pathogenesis. The immunogen that injected to an animal may have a profound on the outer come of the immune responses. Four successive doses of heat killed *H. pylori* (HpHK) antigen was intravenous injected in rabbits at five days a part manner. HpHK antigen stimulate specific mucosal and systemic humoral and cellular immune response determined by raised in the immunoglobulin titers and concentrations, increased the concentrations of C_3 and C_4 which are the complement compartments with significant increased in the lymphoid cells that formed the rosette form , significant migration inhibition index , increased the concentrations of cytokines (IL-4 & IL-8) . HpHk antigen induced positive skin test tuberculin type delayed hypersensitivity, in addition to the histopathological changes at different body organ portions of the animals.

Introduction

The important human pathogen *Helicobacter pylori* (*H. pylori*) causes a persistent gastroduodenal infection that produces a brisk humoral and cellular immune response. The histological characteristics of the mucosal inflammation contain features of both acute and chronic inflammation. (Nurgalieva *et al.*, 2005) *H. pylori* remains one of the most common worldwide human infections and is associated with a number of important upper gastrointestinal (GI) conditions including chronic gastritis, peptic ulcer disease, and gastric malignancy. (Chey and Wong, 2007).

Gastric or duodenal ulcers (commonly referred to as peptic ulcers) are defined as mucosal defects with a diameter of at least 0.5 cm penetrating through the muscularis mucosa. (Dixon, 2001). There are many virulence factors of *H. pylori* that contribute in dissimilar ways to gastric mucosal damage, among them are factors known to be required for the colonization and survival of *H. pylori* in the human stomach. These factors are urease and flagella that are expressed by all *Helicobacter* species (Aguilar *et al.,* 2001 & Belzer *et al*., 2005).

The inflammatory response caused by bacteria colonizing near the pyloric antrum induces G cells in the antrum to secrete the hormone gastrin, which travels through the bloodstream to parietal cells in the fundus. Gastrin stimulates the parietal cells to secrete more acid into the stomach lumen, and over time increases the number of parietal cells, as well. The increased acid load damages the duodenum, which may eventually result in ulcers forming in the duodenum. (Hildreth *et al*., 2008), when *H. pylori* colonizes other areas of the stomach, the inflammatory response can result in atrophy of the stomach lining and eventually ulcers in the stomach. This also may increase the risk of stomach cancer (Palestro *et al*., 2005).

The initial humoral immune response to most bacterial infections involves a humoral IgM response. However, the available data regarding an IgM response among cases of acute *H. pylori* infection are both infrequent and inconsistent. (Nurgalieva *et al.*, 2005)

Intravenous injection with an immunogen prepared from *H. pylori* resulted in cell – cell cooperation could induced the formation of high endothelial venule from the postcapillary venules which served as portal of entry of circulating lymphocytes to the vessels in the site that join to an immune response . (Stites *et al.*, 1994). Lymphocytes (both T cells and B cells), macrophages, neutrophils, mast cells, and dendritic cells (DCs) are usually present (Suzuki *et al*., 2002).

The effective protective immunity against *H. pylori* can be induced in experimental animal models after immunization using various routes of delivery. Vaccination would be a suitable alternative or complement to antibiotic treatment to eradicate the bacteria. A large number of animal experiments have shown that immunization with *H. pylori* antigen in combination with certain adjuvants can prevent and even eliminate *H. pylori* infection (Arora and Czinn, 2005; Xie *et al*., 2007) . This immunogen cause mucosal as well as systemic humoral & cellular immune responses , till now little references regarding the immune status of the lapin animal primed with this bacteria and the time of development of these responses (Kuster *et al.*, 2006).

Objectives

The aim of this study is isolation of *H. pylori* from clinical cases and prepared heat killed antigen (HpHK) from it, then injected this antigen into experimental rabbits via intravenous route to compare between mucosal and systemic humoral and cellular immune responses at different days.

Materials & Methods

1- Specimens

Fifty biopsies specimens were collected from dyspeptic patients suffering from Esophageous ulcer , Acute gastritis , Chronic gastritis , Duodenitis , Gastric ulcer and Duodenal ulcer from both sexes between 20 - 70 years who submitted to endoscopy examination at specialized center of digestive system and endoscopy unit of Medical Marjan City at Babylon governorate during the period from June to September 2010.

2- Bacteria

These biopsies were examined using rapid urease test (RUT) and culture methods. It was found that only four isolates of *H. pylori* were isolated from 50 patients , two isolates were obtained from gastric ulcer and one from each of chronic gastritis and duodenal ulcer respectively.

Bacterial isolates were diagnosed using culture, microscopic and biochemical characteristics according to standard methods. (Holloway *et al.,* 1994; Macfaddin, 2000 ; Kuster *et. al*., 2006 **&** Al-Bermani, 2010)

3- Antigens

Heat killed *H. pylori* (HPHK) antigen was prepared from 24 hour brain heart infusion agar plate culture then we add 6 ml of normal saline to the plats scrape , collect the solution and put it in centrifuge at 4000 rm\ mint for 5 mints, double wash were done with normal saline then compared it with standard opacimeter (WHO) to obtain the concentration equals to 10 IU\ml . The suspension tubes were used after put them in water path at 60 degrees for 30 mints to kill the bacteria and obtained the antigen that was used in immunization the rabbits after done the sterility test. A cell free culture filtrate antigen was also prepared from microaerophilic 72 hour brain heart infusion broth culture of *H. pylori* (Svanborg-Eden *et al*., 1985 & Sachse *et al.*, 2005).

4- Animals

Two groups, each of two rabbits *Oryctalagus cuniculus* were elected , adapted to laboratory conditions and housed under standardized conditions, one served as test & other as control group (Schneider *et al*., 1990).

5- Immunization protocol

Four successive doses of (HpHK) antigen were injected via intravenous route into tested rabbits through four weeks, each dose about 2 ml of antigen that had 10 IU\ml concentrations. Control animals received sterile normal saline in same protocol and this protocol was specific for this research.

6- Mucosal samples and immunoglobulines separation

Gut mucosal samples were obtained from three parts of gut mucosa included esophageous, stomach and duodenum in addition to spleen which is used as lymphoid organ. Then the immunoglobulines were separated from these parts according to (Shnawa and Abid, 2005).

7- Blood Samples

Blood with anticoagulant was processed for E-rosette test and for migration inhibition test. Coagulated blood were collected for the others immunological tests that include: tube agglutination test, measure the concentrations of IgG , IgM ; IL-4 and IL-8 that detected by ELISA test in addition to the concentrations C3 , C4. (**Garvey *et al*., 1977).**

8-Immunology

Agglutination test was performed by microtiteration method, anti *H. pylori* IgG, IgM antibodies were detected by using specialized kits were provided from the (DRG, USA) company . The C_3 and C_4 components were determined by C_3 and C_4 proteins , E-rosette , Capillary Migration Inhibition were perfoemed as in (Garvey *et al.*, 1977), IL-4 and IL-8 cytokines were assayed using ELISA kits (provided from RayBio, USA, Company), skin delayed type hypersensitivity was done as in (Shnawa and Abid, 2005). Histopathology was carried out as in (Kuster *et al.*, 2006).

Results and Discussion

***H. pylori*,** differences in the host response evoked by different strains have been associated with the presence, absence or functionality of several virulence-associated genes, for instance those belonging to the cytotoxin-

associated genes pathogenicity island (cagPAI) and the vacuolation cytotoxin A encoding gene vacA . (**Flahou *et al.*, 2012).**

Infection with *H. pylori* results in robust innate and acquired immune responses by the host, where the gastric epithelium represents a central player. Interaction of *H. pylori* with the host epithelium results in the release of an array of chemokines and cytokines. Some of these factors are stimulated via the engagement of toll-like receptors or cell surface receptors. (Suarez *et al.,* 2006)

The acute antibody and T-cell immune response to *H. pylori* infection in humans has not been studied systematically and the majority of *H. pylori* proteins were those involved in motility and colonization and may represent targets for vaccine development. (Nurgalieva *et al.,* 2005)

Recently, different Th response types induced by *H. pylori* vaccine and their effects in immune response are the main point in the mechanism of *H. pylori* vaccine, indicating that the balance of Th1 and Th2 response is involved in the protection mechanism of *H. pylori* vaccine (Flahou *et al.,* 2012). After immunization, the type of immune response has changed from Th1 to Th2 they found stimulating immune response to Th2 could reduce the number of *H. pylori* and the intensity of inflammation of gastric mucosa, indicating that if the type of immune response induced by immunization has changed from Th1 to Th2, *H pylori* colonization in gastric mucosa can be inhibited by producing Th2 cytokines such as IL-4. However, some studies showed that Th1 and Th2 response together is better than Th2 response only in preventing *H pylori* infection. (Xie *et al*., 2007).

The exact correlation between the common mucosal immune compartments and the attributes of the systemic immune system are conflicting subject or it is somewhat unclear. The correlation between local and systemic immune responses affected by several factors includes : immune gene nature , host susceptibility to replicating or non replicating immunogens, nature of immunization protocol, nature of the host immune system and type of experimental design (Brandtizage and Frasted, 1999). *H. pylori* possess several immunogenic subfractions , such immunogens stimulate B cells , T cells as well as the subset Tdh responsible for hypersensitivity (Velin *et al*., 2004 ; Choi *et al.*, 2011 & Michetti, 2011) .

We studied the development of immune responses at five days (8 , 12 , 16 , 20 and 27) after immunization with HPHK antigen via intravenous route that stimulates *H . pylori* specific humoral systemic and mucosal immunoglobulins titers (Table 1) , also it played an important role in the increased the concentrations of IgG and IgM antibodies in serum and mucosal secretions of immunized rabbits (Table 2). The concentration of C_3 and C_4 which are the complement compartments were significantly increased in the rabbits sera (Table 3).

The bacteria induce a host immune response, but the persistence of the infection suggests that the response is not effective in eliminating the infection. Furthermore, multiple lines of evidence suggest that the immune response contributes to the pathogenesis associated with the infection (Suarez *et al .,* 2006).

The cellular systemic and mucosal immune responses were represented by significant increased in the lymphoid cells that formed the rosette form , significant migration inhibition index with more than 30% inhibition as well (Table 4), furthermore, the HPHK antigen able to inducing tuberculin type delayed hypersensitivity, Hence, their epitopes can be of T dependent type through the activation of Th1 and Th2 (Table 5) (Kayaselcuk *et al*., 2002 ; Velin *et al.*, 2004 & Michetti, 2011).

The chronic immune response induced may be inadequate or misdirected, and could thus afford a colonization advantage for the bacteria by providing improved availability of adhesion places. An example of this is the resulting increase in class II major histocompatibility complex (MHC) and CD74, induced by IFN-γ and IL-8, that are used as receptors by *H. pylori* in addition to see that CD4+ T cell numbers increase in the gastric lamina propria of individuals infected with *H. pylori*. (Suarez *et al .,* 2006)

These cells are predominantly Th1 cells characterized by their production of IFN-γ, because the epithelium separates *H. pylori* from CD4+ T cells, and also expresses key proteins associated with antigen presenting cells, the gastric epithelium, in addition to dendritic cells, could be involved in the presentation of antigens to these CD4+ T cells. The expression of inhibitory B7 related molecules along with CD4+ T cells with a regulatory T cell phenotype could be playing a role in limiting the function of effector CD4+ T cells. (Nurgalieva *et al*., 2005).

Human dendritic cells have been shown to produce IL-8, IL-10, and IL-12 in response to *H. pylori* as well as to purified *H. pylori* antigens. Thus, *H. pylori* can bind to the dendritic cell receptor DC-specific ICAM-3-grabbing nonintegrin (SIGN) through the blood group Lewis X antigen present in its LPS. This interaction can alter the T helper balance and favor pathogen persistence (Suarez *et al .,* 2006).

IL-4 is one of anti-inflammatory cytokines and IL-8 is a proinflammatory cytokine were be detected in serum and mucosal secretions of rabbits with significant increased in their concentrations (Table 6) . Thus *H. pylori* antigens were B and T cells dependent types (Ferrero, 2005 ; Svennerhol**m and Lundgren, 2007).**

The histopathological study was showed the presence of large number of lymphocytes that converted to the plasmocytes with middle to poor infiltration of them in spleen (Picture 1) while the epithelial layer of esophageous, stomach and duodenum had been normal in all treated rabbits.

Table (1) Titers of antibodies in immunized rabbits

Titer						
Types of immune response	Days					Control
	8	12	16	20	27	
Humoral systemic(serum)	10	160	320	640	1280	10
Humoral mucosal						
Esophageous	1	2	8	16	32	1
Stomach	2	4	16	32	64	
Duodenum	1	4	8	16	32	

Table (2) Concentrations of anti-IgG and anti-IgM (Iu\ml) in rabbits immunized with heat killed *H. pylori* antigen

Types of immune response	IgG concentration(Iu\ml) M±S.D.					IgM concentration(Iu\ml) M±S.D.				
	Days					Days				
	8	12	16	20	27	8	12	16	20	27
Humoral systemic(serum)	4.034 ±0.041	4.341 ±0.007	4.348 ±0.016	4.460 ±0.021	4.545 ±0.164	3.577 ±0.002	3.571 ±0.010	3.833 ±0.049	3.813 ±0.005	3.814 ±0.005
Humeral mucosal										
Esophageous	3.726 ±0.006	4.130 ±0.025	4.137 ±0.029	4.342 ±0.309	4.437 ±0.101	2.862 ±0.000	2.940 ±0.001	3.636 ±0.052	3.836 ±0.048	3.636 ±0.043
Stomach	3.928 ±0.003	4.076 ±0.065	4.137 ±0.000	4.340 ±0.312	4.937 ±0.073	3.179 ±0.002	3.177 ±0.000	3.636 ±0.003	3.838 ±0.001	3.813 ±0.004
Duodenum	3.725 ±0.004	4.076 ±0.069	4.137 ±0.246	4.342 ±0.292	4.766 ±0.138	3.020 ±0.001	3.178 ±0.001	3.813 ±0.080	3.973 ±0.104	3.813 ±0.016
Control	4.076 ±0.036					3.638 ±0.001				

Table (3) Concentrations of C_3 and C_4 in rabbits sera immunized with heat killed *H. pylori* antigen

Days	C_3 concentration (mg\dc) M±S.D.	C_4 concentration (mg\dc) M±S.D.
8	140.350±6.293	36.500±0.989
12	149.300±0.000	44.950±1.060
16	156.250±3.323	50.200±0.000
20	158.600±0.000	51.000±1.131
27	185.300±3.535	57.300±1.131
Control	110.500±0.000	37.200±0.000

Table(4) Percentage of E-rosette and LIF in rabbits immunized with heat killed *H. pylori* antigen

Cellular response	Percentage of E-rosette(%) M±S.D.					Percentage of LIF(%) M±S.D.				
	Days					Days				
	8	12	16	20	27	8	12	16	20	27
Systemic	28.150 ±0.919	28.700 ±0.989	30.650 ±0.777	31.500 ±1.202	33.800 ±0.494	96.300 ±0.848	92.700 ±0.707	89.050 ±0.212	83.800± 0.989	80.950 ±0.353
Mucosal										
Esophageous	27.750 ±0.212	29.150 ±0.565	29.700 ±0.000	31.500 ±0.565	33.200 ±0.989	96.050 ±0.212	92.550 ±0.212	86.850 ±0.494	82.700 ±0.565	80.750 ±0.777
Stomach	28.350 ±0.636	30.000 ±0.141	30.850 ±0.070	32.950 ±0.212	35.600 ±1.272	92.750 ±0.212	90.800 ±0.424	89.150 ±0.070	74.750 ±0.777	73.800 ±0.989
Duodenum	27.450 ±1.060	30.200 ±0.989	30.150 ±1.202	32.350 ±0.494	34.800 ±0.424	93.400 ±1.272	90.250 ±0.070	88.850 ±0.353	80.850 ±0.353	78.700 ±0.707
Control	27.500±0.427					93.500±0.427				

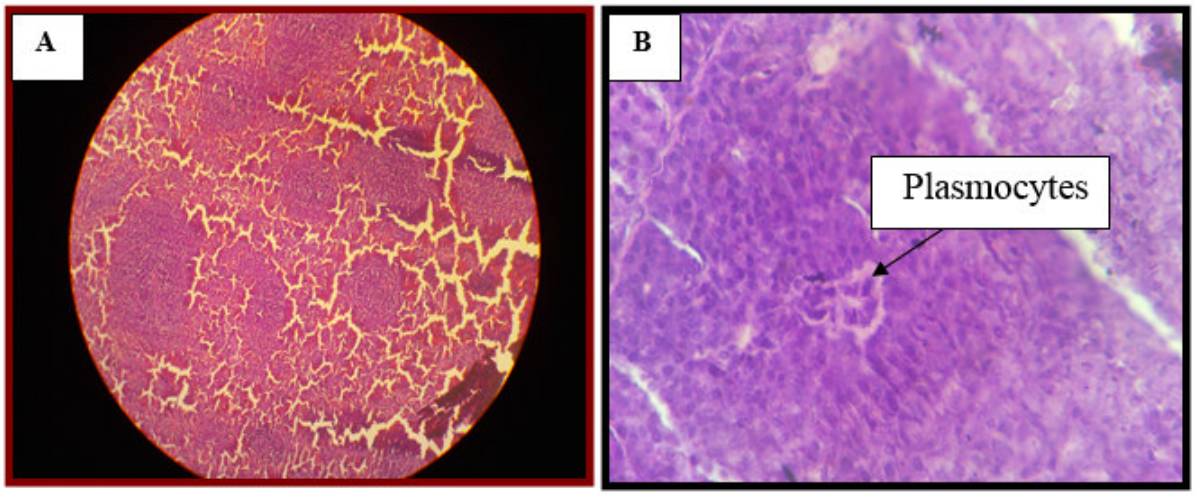
Table (5) Skin test of rabbits immunized with Heat killed *H. pylori* antigen

Date of inoculation CFC \ Days	Skin test \ Hours					Immune reaction
	6	18	24	48	72	
6	-	E	E	EI	EI	Notes
	-	-	-	5	5	Reaction area (mm)
10	-	E	EIN	EIN	EIN	Notes
	-	-	11	11	11	Reaction area (mm)
14	-	E	EIN	EIN	EIN	Notes
	-	-	15	15	15	Reaction area (mm)
18	-	E	EI	EI	EI	Notes
	-	-	11	11	11	Reaction area (mm)
25	-	E	E	E	E	Notes
	-	-	-	-	-	Reaction area (mm)

- With negative results for all control groups .
N- Necrosis, I- Induration, E- Erythema.

Table (6) Concentrations of IL-4 & IL-8 (pg\ml) in rabbits immunized with Heat killed *H. pylori* antigen

Types of immune response	IL-4 concentration(pg\ml) M±S.D.					IL-8 concentration(pg\ml) M±S.D.				
	Days					Days				
	8	12	16	20	27	8	12	16	20	27
Humeral systemic(serum)	9.668 ±0.147	12.076 ±0.316	12.080 ±0.107	14.016 ±0.165	29.936 ±2.456	18.428 ±0.569	18.896 ±0.943	19.876 ±0.216	20.520 ±0.726	20.540 ±0.643
Humeral mucosal										
Esophageous	6.280 ±0.083	6.764 ±0.124	7.272 ±0.202	7.720 ±0.855	7.000 ±0.251	17.908 ±4.050	19.896 ±0.340	21.552 ±0.103	21.552 ±0.149	23.232 ±0.009
Stomach	7.000 ±0.062	7.404 ±0.111	7.732 ±0.230	8.200 ±0.231	7.152 ±0.165	19.796 ±0.469	19.932 ±0.114	24.200 ±0.271	24.876 ±0.265	24.888 ±0.094
Duodenum	6.916 ±0.038	7.000 ±0.203	7.936 ±0.165	8.200 ±0.275	6.839 ±1.110	16.584 ±0.340	19.920 ±0.063	21.552 ±0.117	21.552 ±0.117	21.564 ±0.284
Control	7.004±0.012					19.814±0.050				



Picture (1) Section in spleen of rabbits immunized with Heat killed *H. pylori* antigen : A- control grope , B- plasmocyte (100X,400X,1000X)

Conclusions

According to the results of this study we can conclude that serum and mucosal anti *H. pylori* antibodies elevated, serum C_3 & C_4 levels , lymphocytes & their secretion of cytokines were correlated to the status of *H. pylori* immunity & protection against recurrent infections.

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