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Research Article

Evaluation of *Helicobacter pylori* Infection in Rheumatoid Arthritis Patients and Its Correlation to Disease Severity

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ABSTRACT

Background: Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease which is recognized by symmetric inflammation of joints. Many factors have been proposed as its etiology including microbial infections. *H. pylori* have been considered as one of the infectious agents linked to RA; however, the data regarding this relation is controversial.

Aim of work: The aim of the study to evaluate the relationship between rheumatoid arthritis severity and *H. pylori* infection in rheumatoid arthritis patients.

Patients and methods: A cross sectional study was conduct at Al-Azhar University Hospital (Assuit) on one hundred patients (10 male, 90 female) diagnosed as rheumatoid arthritis according to ACR 1988, these patients were selected from inpatient and outpatient clinics of Internal medicine and rheumatology department. Those patients were divided according to *H. pylori* stool antigen into two groups , Group 1 includes 50 rheumatoid arthritis patients positive for *H. pylori* stool antigen and Group 2 also includes 50 rheumatoid arthritis patients negative for *H. pylori* stool antigen. All patients undergone to detailed history taking, full clinical examinations included musculoskeletal examination, laboratory and radiological investigations to detect the severity of rheumatoid arthritis and its relation to *H. pylori* infection.

Results: Our study show that rheumatoid arthritis patients with positive *H. pylori* stool antigen had had higher disease activity markers than negative patients.

Keywords: *Helicobacter pylori*; Rheumatoid arthritis; Bacteria; Colon; Stool

INTRODUCTION

Helicobacter pylori are a widespread, gram-negative bacterium which usually infects the gastric mucosa. Since its initial detection as a human pathogen in 1983, *H. pylori* have been associated in numerous diseases. *H. pylori* infection is widely prevalent throughout worldwide, Frequency of *H. pylori* infection is approximately 80% in underdeveloped countries compared to 50% in developed parts of the world, correlating the disease prevalence with poor socioeconomic status [1,2]. The way *H. pylori* infection is transmitted is still unclear. Interpersonal transmission appears to be the main route, although environmental transmission, such as drinking contaminated water and Parental transmission has been frequently reported [3]. As in many chronic infections, most individuals remain asymptomatic with only a small proportion developing clinical disease. *H. pylori* are considered a pathogen as it universally causes progressive inflammation and gastric mucosal damage [4] as shown in Figures 1 and 2. The role of *H. pylori* infection is explored in more and more extra-gastric diseases including rheumatic disorders [5]. The immune response to *H. pylori* occurs in patients concurrently infected with Mycobacterium tuberculosis or helminthes [6]. Also the occurrence of a concomitant decline in the prevalence of both heart attacks and

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duodenal ulcers due to the interference with *H. pylori* eradication [7] as that chronic *H. pylori* infection is significantly associated with high levels of glycated hemoglobin A1c and type 2 DM in patients over 65 years old and decreased levels of insulin and insulin sensitivity in subjects under 45 years old [8] also, the prevalence of *H. pylori* in patients with iron deficiency anemia is higher compared with that of the general population [9] and occurrence of cirrhotic nodules and liver fibrosis in patients coinfected with *H. pylori* and HCV [10].

In rheumatic disorders *H. pylori* has been associated with autoimmunity, a chronic infection with H. *pylori* initiates' antigenic process and can induce systemic inflammatory response [11]. *H. pylori* antigens were found to activate cross reactive T cells which can lead to autoimmune gastritis, Chronic stimulation of B cells with urea's produced by *H. pylori* could generate auto-antibodies including IgM rheumatoid factor [12]. Patients with rheumatoid arthritis often develop ulcers induced by NSAID that used, and *H. pylori* may play a more minor role in inducing gastro duodenal ulcers in patients with rheumatoid arthritis than in patients without such a disease [13].

MATERIALS AND METHODS

This cross section study was conduct in Al-Azhar University Hospital (Assuit) on one hundred patients (10 male, 90 female) diagnosed as rheumatoid arthritis according to ACR 1988 (American College of Rheumatology 1988 Criteria) were selected from inpatient and outpatient clinics of Internal medicine and rheumatology department, in the period between November 2015 to October 2016 . Patient was classified into two groups according to *H. pylori* stool antigen:

Group 1

50 rheumatoid arthritis patients positive for *H. pylori* stool antigen (3 male, 47 female).

Group 2

50 rheumatoid arthritis patients negative for *H. pylori* stool antigen (7 male, 43 female).

For classification purposes, a patient is said to have RA if he or she has satisfied at least four of the seven criteria. Criteria 1 through 4 must be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is not to be made [14]. Any patient with the following criteria was excluded from the study:

- Patient's undergone surgical synovectomy in any large joint.
- Patient's undergone surgery of the gastrointestinal tract, which had an active peptic ulcer.
- Patient with chronic diarrhea.
- Patients who had history of long term use of chemotherapy for GI diseases.
- Patient's with GI malignancies and GI bleeding disorders.
- Patients who had unstable cardiac or pulmonary disease.
- Patients with other autoimmune diseases.
- Patients with DM or hyperuricemia.
- Patients with heavy smoking.

This study were evaluated and approved by the Ethical Committee of Al-Azhar University Hospital (Assuit) after being informed on the purpose and procedures of the study, all subjects signed an informed consent form. All patients were subjected to the following:

History taking

Personal history: Name, age, gender, occupation, residence and marital status.

Complaint and its duration: Taken in the patient's own words.

Present history: Detailed inquiry concerning the involved joint structures, including:

- Mode and date of onset, Symmetry, Precipitating factors, Course and duration of the disease, Sequence and pattern of joint involvement, Morning stiffness of the hands (duration in minutes), Number of swollen and tender joints.
- History of GIT disease (chronic diarrhea, active peptic ulcer, surgery malignancies, GI bleeding disorders).

Past history: Previous history of blood transfusion, hospital admission, joint trauma or fracture.

Family history: History of similar condition.

Clinical examination

General examination: Includes-

- Pulse, blood pressure and temperature.
- Eye and mouth examination.
- Chest and Heart examinations.
- Abdominal examination.

Locomotor system examination: Includes-

- Joints of the body were examined by routine physical examination that included inspection, palpation, movement and special tests.
- Specific joints that were examined included those 28 joints that are used in the DAS 28 formula and include the following: right and left shoulder joints, right and left elbow joints, right and left wrist joints, right and left MCP joints, right and left PIP joints, right and left knee joints.
- Joints were examined for both tenderness and swelling due to sinusitis.

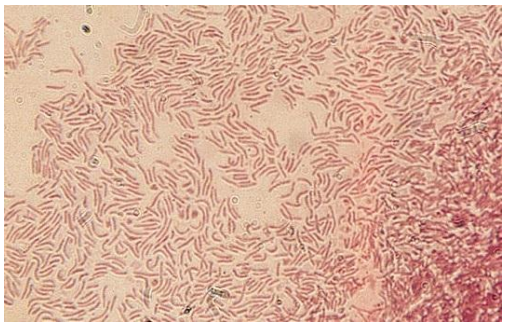

Figure 1: *Helicobacter pylori* gram stain from culture.

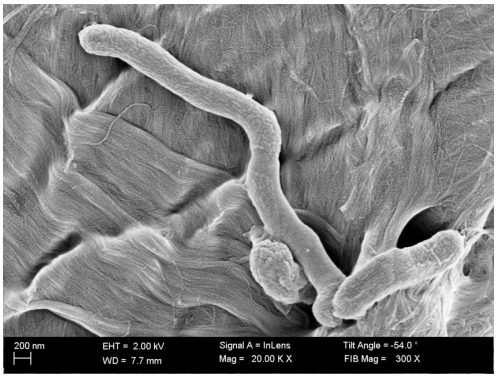

Figure 2: Morphological forms of *H. pylori* observed by scanning electron.

Investigations

Laboratory investigations: Included-

- CBC Automated Differential Cell Counters is a quantitative, automated hematology analyzers and leukocyte differential cell counters.
- Liver function tests example- ALT, AST, Bilirubin and Alkaline phosphatase was evaluated by colorimetric method Using Hitachi, 911 automatic analyzer.
- Kidney Function tests example- Serum creatinine, blood urea Using Hitachi, 911 automatic analyzer.
- Fasting and 2 hours. Postprandial blood sugar level.
- RF titre (by Rose Waaler method) [15].

Investigations for *Helicobacter Pylori* infection:

Fecal Antigen Test (FAT): This identifies H.pylori antigen level in stool by ELISA, which was done before and after treatment [16].

Investigations for disease activity evaluation.

- ESR, Normal values (Males 0-10 mm 1st hour and Females 10-20 mm 1st hour) [17].
- CRP titre these use the techniques of immunonephelometry or immunoturbidimetry [18].

Radiological investigations: Radiographic examination of the hands was done by:

- Plain X-ray of both hand (P.A) view.
- Power Doppler (PD) Ultrasound on the hand: by a commercially available ultrasound real-time scanner using multi frequency linear transducer (DIASUS with 5-10 MHZ linear probe).

All radiographic sign were detected by an experienced observer, unaware of the clinical and laboratory data, and compared between Fecal Antigen positive and negative subjects.

Disease activity evaluation using modified DAS 28: The Modified Disease Activity Score 28(DAS28) [19] includes the following parameters:

- Tender joint count in 28 joints
- Swollen joint count in 28 joints
- ESR

The modified DAS is calculated using the following formula:

$DAS28=[0.56 \times \sqrt{(28\ TJC)}+0.28 \times \sqrt{(28\ SJC)}+0.70 \times \ln(ESR)] \times 1.08+0.16.$

Or $DAS28=0.56 \times \sqrt{(TJC28)}+0.28 \times \sqrt{(SJC28)}+0.70 \times \ln(ESR)+0.014 \times$ (General Health).

The level of disease activity can be interpreted as:

- Low (DAS28) ≤ 3.2
- Moderate 3.2<(DAS28) ≤ 5.1
- High (DAS28)>5.1

A DAS<2.6 corresponds to being in remission. Both groups were assessed for RA activity to see if there was significant difference between them.

Statistical analysis

Results were collected, tabulated, statistically analyzed by IBM personal computer and statistical package SPSS version 16 [20]. Two types of statistics were done:

Descriptive: For example- Percentage (%), range, mean and standard deviation SD.

Analytical: Includes-

- It is a single test used to collectively indicate the presence of any significant difference between two groups for a normally distributed quantitative variable.
- Significant difference if p<0.0, non-significant difference if p>0.05, highly significant difference if p<0.001.

RESULTS

- The present study showed the following results:
- The studied groups of patient's age ranged (37.3 ± 10.1) years with RA disease duration of (8.47±6.31) years.
- There was no statistically significant difference between fecal antigen positive and negative groups according to age, sex and rheumatoid arthritis disease duration (p-value>0.05).
- The fecal antigen positive group had significantly prolonged period of mourning stiffness , higher numbers of tender and swollen joints and elevated disease activity scores than the negative group at the start of study (p-value<0.05).
- Regarding the laboratory measures, the positive group had significantly higher CRP levels and serum RF titers than the negative one (p-value<0.05). On other hand no significant difference between the two groups according to hemoglobin level, platelet count and WBCs count.
- Regarding the radiology measures, the positive group had significantly higher disease activity as regard joint space narrowing, joint erosion, joint synovitis, doppler activity and deformity than the negative one (p-value<0.05).
- Regarding doppler activity there was statistically significant difference between the two groups where positive cases has higher doppler activity, (p-value<0.05) at the start of study.
- Regarding DAS 28 Scoring, positive cases have statistically higher score than negative group. (p-value<0.05) at the start of study.

DISCUSSION

Helicobacter pylori are a gram-negative, flagellated bacterium which was first isolated in 1983 by Warren and Marshal. It is widely prevalent with approximately 50% of the Western world and over 80% of those living in developing countries infected with the bacterium [21]. Evidence for the involvement of infectious agents in autoimmune diseases, such as SLE and RA remains controversial [22]. Chronic infection with *H. pylori* serves as a source of persistent antigenic stimulation and underlies the pathogens ability systemic inflammatory response. The prolonged interaction between the bacterium and host immune mechanisms makes *H. pylori* a plausible infectious agent for triggering autoimmunity [23]. Autoantibodies, such as IgM rheumatoid factor, anti-single stranded DNA antibody and antiphosphotidyl choline antibodies, were demonstrated to be produced by B cells after their activation by *H. pylori* components, particularly urease [12]. In addition, a number of viral and bacterial pathogens such as, Epstein-Barr virus EBV, parvovirus B19, Hepatitis C virus, Proteus mirabilis, and Mycobacterium tuberculosis, may have a role in disease pathogenesis as well [24]. The association of *H. pylori* infection in the pathogenesis of RA is controversial. As the incidence of upper gastro-intestinal tract lesions is significantly higher in patients with rheumatoid arthritis [25]. In spite that our study did not investigate the prevalence of H.pylori infection among RA patients, the prevalence of *H. pylori* infection in rheumatoid arthritis patients in different studies reported that, Zentilin and his colleagues who showed that the prevalence of *H. pylori* infection in 58 rheumatoid arthritis patients with dyspeptic symptoms was 48% [26]. In our study we found that there was no significant difference in age between both H.pylori FAT positive and negative groups. This is in agreement with Graff and his colleagues who reported that there was no significant difference regarding age when comparing *H. pylori* positive with *H. pylori* negative patients [27]. In our study and regarding gender, positive titre was common in females than males. This may be due to higher prevalence of RA in females than males, and not actually related to the infection predilection. This comes in contradiction with the study performed by Graff and his colleagues which reported that there were more *H. pylori* seropositive men than women, although this was statistically insignificant [28]. On the other hand Nakamura and his colleagues found that the gender of RA patients did not affect *H. pylori* status [29]. In our study the positive group has longer RA disease duration than the negative group but the difference was not significant this comes in agreement with Ishikawa and his colleagues who found that in a study on 184 RA patients, the disease duration was not different between *H. pylori* positive or negative patients [13]. In our present study we found that there was a significant difference ($p<0.033$) in the duration of morning stiffness in H.pylori FAT positive and *H. pylori* FAT negative patients. This is in agreement with Graff and his colleagues who reported that the duration of morning stiffness was significantly longer in *H. pylori* positive than in *H. pylori* negative patients ($p<0.04$) [28]. In our study we found that there was a significant difference was found between *H. pylori* FAT positive and negative groups regarding the tender joint count and swollen joints count. This go with Graff and his colleagues who reported that the *H. pylori* positive patients has tender joints count and swollen joints count higher than the negative group however this was not significant [28]. In contrast with the study performed by Zentilin and his colleagues, they found that there was no significant difference between H.pylori positive and negative groups regarding the number of tender and swollen joint count [26]. In our study we found that, the FAT positive group has significantly higher level of C-reactive protein than the negative group at baseline ($p<0.001$). This comes in agreement with Zentilin and his colleagues who showed that there was a highly significant difference regarding the C-reactive protein level ($p<0.0001$) between *H. pylori*-positive and *H. pylori*-negative rheumatoid arthritis patients at baseline [26]. In our study we found that, the FAT positive group had higher level of RF titre at baseline than the negative group however the difference was not significant ($p<0.177$). This result was different from that obtained by Nakamura and his colleagues' study on 97 RA patients who found that the presence of a rheumatoid factor was inversely related to *H. pylori* infection, and the value of the rheumatoid factor was lower in patients with the infection [29]. On the other hand, we found that, the FAT positive group has significantly higher disease activity score as DAS28 than the negative group. This comes in agreement with Hongyan and his colleagues who found a higher prevalence of CRP with DAS28 ($p<0.034$) among RA patients with H.pylori infection [30]. Also, we found that, the FAT positive group has significantly higher disease activity as regard of joint space narrowing ($p<0.001$), joint erosion ($p<0.008$), joint synovitis, Doppler activity and deformity (p-value<0.05) than the negative group. Published studies evaluated the sensitivity to change of PDUS in the evaluation of the response to biological drugs, showing a significant reduction of joint inflammation, as evaluated by GS or PD assessment, and significant correlations with disease activity indices, such as the Disease Activity Score (DAS28) [30]. Lastly, the exceeding findings appear to suggest a pathogenetic role of *H. pylori* in RA. It is associated with a higher disease activity; it may contribute to conserve an inflammatory condition in response to the continuous antigenic stimulus induced by chronic infection [5].

CONCLUSION

The present study concluded that, rheumatoid arthritis patients positive with *H. pylori* infection has higher disease activity markers than negative patients. So, eradication of *H. pylori* infection in positive rheumatoid arthritis patients may lead to decrease disease activity in those patients. The present study concluded that, rheumatoid arthritis patient's positive with *H. pylori* infection has higher disease activity markers than negative patients. So, eradication of *H. pylori* infection in positive rheumatoid arthritis patients may lead to decrease disease activity in those patients.

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