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The possible association between Helicobacter Pylori Infection and the severity of rheumatoid arthritis in Egyptian patients.

Neveen Rashad Mostafa[1*], Abeer Ahmed Mohamed Ali[2]

1) Associate professor, department of Internal Medicine Medical Research Institute, Alexandria University, Egypt.
2) Associate professor, department of Chemical pathology Medical Research Institute, Alexandria University, Egypt.

ABSTRACT:
Background: The etiology of the autoimmune diseases is not clear, but some contributing elements may activate its evolution in hereditary susceptible person, like some viral or bacterial infection or chemical exposure.
Helicobacter pylori is a Gram-negative organism that affects mostly people in developing countries (80%) and a percentage of people in developed countries (50 %).
This organism as a chronic infection can induce a state of chronic inflammation that may trigger the appearance of autoimmune diseases or aggravates their clinical course.
One of the most common autoimmune disorders is rheumatoid arthritis that is thought to be initiated or aggravated by chronic infection. In the present study, the relation between rheumatoid arthritis and Helicobacter pylori infection will be examined.
Aim: Compare the progression of rheumatoid arthritis in patients with and without infection with Helicobacter pylori.
Patients &Methods: 50 rheumatoid arthritis patients were confirmed to have positive serum IgG antibodies to Helicobacter pylori, provided that no past history of previous infection or previous treatment of Helicobacter pylori. All patients were assessed for the severity of rheumatoid arthritis through the estimation of their ESR and CRP levels and by using the DAS 28/ESR score.
Results: No significant effect of infection with H pylori on ESR, CRP, or DAS28/ESR.
Conclusion: Assessment parameters of rheumatoid arthritis activity and severity were not affected by the existence of H pylori infection.

Keywords: Autoimmunity, Rheumatoid arthritis, Inflammation, Helicobacter pylori, infection.

INTRODUCTION

Rheumatoid arthritis (RA) is a long-standing disease that results in pain; swelling and morning stiffness usually affecting the small joints (hand, feet), and wrist. [(1)] RA is complex disease that represents interplay between self and environmental elements that determine the disease susceptibility, course, and severity. Self-factors can be divided into genetic;hormonal or neuroendocrinal. However, environmental factors include smoking; chronic infections; nutrition; and socioeconomic level. [(2)]

Some known viral and bacterial pathogens can trigger the development of RA like, Epstein-Barr virus, parvovirus B19, Hepatitis C virus, , Proteus, and mycobacterium tuberculosis.[(3)] The mechanism by which the infectious agents can cause autoimmune diseases include microbial super-antigens, non-immune cell expression of MHC class II, molecular mimicry, formation of immune complex, direct inflammatory injury, persistently elevated cytokines like interferon (IFN)-γ, and disproportionate T-regulatory/Th17. [(4)]

Helicobacter pylori (H pylori) is a gram-negative, extracellular bacterium, and observed to be a wide spreading chronic infection all over the world. [(5)] Persistent H pylori infection induces immune activation that results in prolonged signaling of cytokine and gastric mucosal aggregation by lymphocytes, neutrophils, and macrophages. Moreover, there is induction of antibody formation and generation of effector T cells because it provides continuous antigenic stimulation. [(6)] As a result, it is thought that H pylori can be connected to many autoimmune disorders and claimed by some authors to be implemented in the pathogenesis of RA.[(7)]

Although some studies investigated the relation between H. pylori infection and development of RA, some of them found a strong association, but the others reported negative results. [(8)] Because of these conflicting results, and due to the burden of RA disease with its disabilities and systemic complications, and the importance of early detection of RA, we examined the impact of H pylori

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*Corresponding author:*Neveen Rashad Mostafa

infection on the clinical course of RA.

Methods

Study design: Prospective randomized clinical trial conducted on fifty patients with RA, appear at the outpatient clinic of the Medical Research Institute hospital during time between July 2023 and January 2024, patients were tested for the existence of H pylori infection through detection of serum-specific immunoglobulin G, severity of RA were evaluated using DAS 28/ESR and by estimating ESR and CRP levels. All Participators had signed the informed consent, after approval of the local Ethics Committee of the Medical Research Institute that follows the Helsinki Declaration's Requirements.

Patients:

Inclusion criteria: Seropositive rheumatoid arthritis patients shared in the research after fulfillment of the diagnostic criteria based on the American College of Rheumatology recommendations. [9]

Exclusion criteria: Anemia, malignancy, Liver failure, renal failure, active infection, and other autoimmune diseases, previous diagnosis or treatment of H pylori infection.

Clinical data and laboratory investigations.

- Clinical examination**.**

The 28 joints incorporated in DAS 28 were tested for both tenderness and swelling, they include bilateral examination of the wrist joint, elbow joint, shoulder joint, metacarpophalangeal joints, proximal interphalangeal joints, and knee joint.

- Estimation of ESR, and CRP as markers of inflammation. [10]
- DAS28/ESR was calculated as follow :

DAS28= [0.56 × √ (28 TJC)+0.28 × √(28 SJC)+0.70 × ln (ESR)] × 1.08+0.16.

<2.6 is the cutoff value for remission. [11]

- ELISA method was used to assess anti-H pylori IgG antibody titre in the patient's serum. [12]
- Other laboratory tests include Liver and renal profiles and complete blood count. [13]

Statistical analysis of the data

IBM SPSS software package version 20.0 was the computer programmer that used for data analysis. Categorical data were expressed as numbers and percentages, Chi-square test was used for comparison between two groups, quantitative data were expressed as mean and standard deviation, student t-test was used to compare between quantitative variables (normally distributed). P value is the test significance at the 5% level.

Results

This study was running on 50 patients with confirmed RA and tested for the existence of H pylori infection, RA severity, and activity were assessed in all patients with or without infection.

H pylori infection was confirmed in 22 patients (44%), 27 % were males and 73% were females. H pylori infection was absent in 28 patients (56%), 25% were males and 75 % were females. Gender was matched in all patients. (Table 1)

The mean age of H pylori-infected patients was 46.3 ± 2.5 yrs, and in patients without infection the mean age was 58.6 ± 3.1 yrs, significant low mean age was noted in H pylori positive patients in comparison to H pylori negative patients. P= <0.001 (Table 1)

Table 1: Distribution of the studied cases in relation to age and gender.

	H pylori positive n=22	H pylori negative n=28	Test of significance	P
Age Mean ±Standard deviation	46.3 ± 2.5	58.6 ± 3.1	Student t-test = 15.132*	<0.001*
Gender				
Male	6 (27%)	7 (25%)	Chi square test (χ^2) = 0.033	0.856
Female	16 (73%)	21 (75%)		

* Significant difference by student t-test at p≤0.05

The activity of RA was assessed by estimating the levels of ESR and CRP in all patients. ESR level was higher in H pylori positive patients (35.7 ± 16.6mm/hr) than in H pylori negative patients (33.7 ± 20.3 mm/hr) but the test results were not significant. P=0.710 (Table 2)

Similarly, CRP level was higher in H pylori-infected patients (12.3 ± 3.4mg/dl) than in patients without infection (10.79 ± 3.3mg/dl), but this result had no statistical significance. P=0.120 (Table 2)

RA severity was assessed using DAS28/ESR score, with a remission cutoff value < 2.6, In H pylori positive patients the mean score was (3.3 ± 1.1), while in H pylori negative patients, the mean score was (3.7 ± 1.2), the mean score didn't show any significant difference among all RA patients. P=0.231 (Table 2)

Table 2:Comparison between H pylori positive, and H pylori negative patients according to ESR,CRP and DAS 28/ESR

	H pylori positive n=22	H pylori negative n=28	Student t-test	P
ESR (mm/hr)	35.7 ± 16.6	33.7 ± 20.3	0.374	0.710
CRP (mg/dl)	12.3 ± 3.4	10.79 ± 3.3	1.585	0.120
DAS28/ESR	3.2 ± 1.2	3.7 ± 1.2	1.213	0.231

Data presented as Mean ±Standard deviation

Discussion:

Helicobacter pylori are Gram-negative organisms that have infected most people in developing countries and a large percentage of people in developed countries. A short time ago, H pylori was claimed to be connected with many extragastric disorders such as cardiovascular diseases, insulin resistance, and autoimmune diseases. [(14)] The chronic nature of H pylori infection allows the organism to be the origin of continuous antigenic stimulation provoking immune response. The urease component of H pylori can stimulate B cells to produce autoantibodies and trigger autoimmunity, one of these autoantibodies is IgM rheumatoid factor, because of this it was thought that H pylori infection take part in the development and worsening of rheumatoid arthritis. [(15)]

Many studies found that the age of RA patients that have the highest rate of H pylori infection was 41-49, this was found in the study by Pshtewan D. [(16)] and the study by Ibrahim S, [(17)] who found the greater rate of H pylori infection (28%) was in the age between 40-49 years, some other studies found no difference in mean age between H pylori positive patients and H pylori negative patients. [(15)] In the present study, the infection rate was more in the mean age of 46.3 ± 2.5 yrs.

The same study by Pshtewan D. [(16)] established that H pylori infection incidence was more in females (64%), than in males (36%), also Ibrahim S, [(15)] found the rate of infection in females (60%) and in males (40 %), but Graff et al, [(18)] Found H pylori IgG was higher in male patients with RA than Females but there was no statistical significance. This is because RA is more common in females. In this study, the number of females with RA was higher than in males but gender distribution was matched in all participants (P= 0.856)

In a large retrospective cohort study, 97533 H pylori-infected patients were followed up during the period between years 2000-2017. They found a high incidence of RA in both male and female patients infected with H pylori, especially in patients aged <30 years. [(19)]

Ebrahimi et al. [(20)] studied the influence of H. pylori infection on the clinical progression of RA, they examined the level of H pylori antibody titer, H pylori antigen in stool, and CagA protein. Many inflammatory markers were remarkably higher in those with H pylori infection especially those who have CagA protein, but they didn't find any significant difference in DAS 28 score between infected and non-infected patients.

In another recent study, forty patients with RA, 20 patients have H. pylori infection, and 20 patients without H. pylori infection, the evaluation of all patients started at the beginning of the study, and every 3 months afterward, H pylori diagnosis, and confirmation of eradication were done using a stool antigen test. Over the whole duration of follow-up, patients with H pylori infection showed more severe joint inflammation and tenderness with an increased number of joints affected, also visual analog scale, DAS 28/ESR, and DAS/28 CRP scores were increased in patients with H pylori infection. However, no difference in laboratory tests (CRP, ESR) or clinical parameters have been changed after H pylori has been eradicated which made the investigator concluded that the association between the infection and the progression of RA does not exist. [(21)]

Bartels et al, [(22)] in their study which involved 56000 divided the patients into patients with H pylori positive test and patients without H pylori negative test, the patients were followed up for 8 years, they found no increased incidence of RA in H pylori positive patients and the study failed to find any relation between them. Youssefi et al. also couldn't find any connection between H pylori and RA and they come to an end that the infection is not linked to the clinical course of RA. [(23)]

In our study, inflammatory markers (ESR, CRP) levels were higher in patients with H pylori positive test than in patients negative test, but this was not statistically significant, also clinical parameters used to evaluate the severity of RA (DAS 28/ESR) showed a higher score in Rheumatoid patient with H pylori positive test than in patients negative test, but also without any statistical significance. This may be explained by the fact that patients with RA are usually on anti-inflammatory medications and immunomodulators, these types of medications can control the production of mediators and limit the release of cytokines and interleukins that are usually released by the body as a reaction to H pylori infection. [(24)]

Conclusion

H pylori can induce a state of chronic inflammation but this has no effect on the clinical course or severity of rheumatoid arthritis

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