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ORIGINAL ARTICLE

Assessment of *H. pylori* seropositivity in Multiple Sclerosis and its Relationship with Disease Severity in Egypt

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ABSTRACT

Background: *Studies have shown that H.Pylori might have a protective role in Multiple Sclerosis MS. However, there are inadequate and inconsistent epidemiological data regarding H. pylori serology among MS patients in Egypt.* ***Objectives:*** *We aim to measure and analyze the serum level of IgM and IgG of H. pylori among different clinical subsets of MS and to correlate it with the number of relapses, duration of disease, Disease Modifying Therapy (DMT) and Expanded Disability Status Scale EDSS. Methods: This is a case-control study that included 22 patients with SPMS secondary progressive multiple sclerosis and RRMS relapsing remitting multiple sclerosis and 22 control were recruited. The study comprised patients with a confirmed diagnosis of MS in accordance with the 2017 revisions to McDonald's criteria.* ***Results:*** *H. pylori immunoglobulin M IgM and IgG seropositivity in cases and control groups showed no significant difference among both groups.* ***Conclusion:*** *There was no insignificant association between the H. pylori antibodies and MS. Studies with a larger sample size are required to support our findings even more.*

INTRODUCTION

The central nervous system CNS is impacted by MS, an autoimmune neurodegenerative disease [1]. Previously, using the global burden of disease GBD, there were 2.2 million MS patients worldwide, with 19 thousand deaths documented. MS is classified into four clinical types: There are four types of relapsing-remitting depression: primary-progressive, secondary-progressive, and progressive-recurrent[2]. Using an age-period-cohort analysis, researchers assessed the global, regional, and national burden of MS from 1990 to 2019. They discovered that the number of new cases, fatalities, and disability-adjusted life years DALYs linked with MS increased globally throughout this time period, whereas the age-standardized rate ASR dropped [3].

Recent treatment options for MS remain insufficient[4]. Although its exact pathogenesis is unknown, MS is linked to intricate interplay between genetic and environmental variables [5]. According to the "hygiene hypothesis," exposure to specific microbes as a child may have a preventive effect against developing allergies and autoimmune illnesses[6,7]. In this context, *H. pylori* was debated to be related to MS disease [7, 19]; as a higher prevalence of *H. pylori* has been linked to a number of CNS neurological disorders, including cerebrovascular diseases, moderate cognitive impairment, seizure disorders, migraine, Alzheimer's disease AD, Parkinson's disease, MS[8], and acute inflammatory polyneuropathies AIP [9]. Studies revealed a relation between *H. pylori* and MS, but with contradicting results.

H. pylori; A gram-negative bacteria begins to colonize the stomach in infancy and affect around half of the population worldwide [10]. The highest prevalence being in the developing countries, while a reduced incidence is reported in the western countries [11]. Almost all the infected patients remain asymptomatic, peptic ulcer, low-grade stomach mucosa-associated lymphoid tissue MALT lymphoma, and gastric cancer are all linked to H pylori [12].

H. pylori infection was believed to be protective against MS, and in a Japanese study, it was discovered that MS patients had lower *H. pylori* prevalence than the general population. Additionally, it was discovered that *H. pylori* seropositivity and illness severity were

inversely related [13]. Another study reported the inverse relation where increased *H. pylori* prevalence was noted among MS patients [14].

The accessibility of serological data containing the exposure history for multiple infectious agents for a large number of adults in their middle to late twenties would allow for the retesting of putative associations and the identification of novel associations between infectious agents and multiple disease outcomes while accounting for potential confounders. Even in modest numbers, serial follow-up measures may help increase understanding of changing exposure risks in the cohort over time [15].

We aimed to analyze the seropositivity of *H. pylori* among different clinical subsets of MS and to correlate it with the number of relapses, duration of disease, Disease Modifying therapy DMT and Expanded Disability Status Scale EDSS.

METHODOLOGY

The study was carried out as a case-control study. It was conducted at the Neurology and Clinical Pathology Department labs at Suez Canal University Hospital, Egypt, Ismailia. An Informed consent was obtained from all the patients. The target population included patients attending the Outpatient Neurology Clinic a convenient sample of patients with MS was used in this study. The Sample population included two groups: 1: Study group; twenty-two patients with a diagnosis of MS according to the 2017 revised McDonald's criteria. 2; Control group; twenty-two subjects of similar age and sex were matched to the study group, they were genetically unrelated friends or spouses of the patients who had no objective clinical signs of neurological disease, no diagnosis of MS, and no known case of MS in the family. All MS patients had thorough hospitalization medical records that included information on their age, sex, age of onset, symptoms, and signs, as well as the results of MRIs and the EDSS scale. These scans were assessed by a specialized neurologist, The MRI brain scans were performed using Siemens 1.5-tesla MRI scanner Siemens, Germany. Slices from the axial scans were 3 to 5 mm thick. The supratentorial, infratentorial, and overall distribution of the plaque in the brain were evaluated by the same neurologist. The study comprised patients with a confirmed diagnosis of MS in accordance with the 2017 revisions to McDonald's criteria; while patients with history of or showing evidence of other neurological disorders, psychiatric disorders, Clinically Isolated Syndrome, or those suffering from any chronic illnesses were excluded from the study. All the 44 participants were examined for the presence of IgG and IgM antibodies Abs against *H. pylori* in their serum sample using ELISA kits Euroimmun, Lubeck, Germany. A measure of IgG was considered negative at a cut-off value of <0.75, equivocal at 0.75 – <1 and positive at ≥1, while a measure of IgM was considered negative at a cut-off value of ≤30, equivocal at 30 - < 40 and positive at ≥ 40.

Approval from the Medical Research Committee of Faculty of Medicine, Suez Canal University was obtained **Research5216#, 21-2-2023**; complied with local legislation and the Declaration of Helsinki, and informed consent was obtained from each participant in the study.

STATISTICS

The data analysis was done using IBM SPSS software, version 20.0 Armonk, NY: IBM Corp. The qualitative data were represented using numbers and percentages. The Shapiro-Wilk test was used to determine whether the distribution was normal. Quantitative data were displayed using the range minimum and maximum, mean, standard deviation, median, and interquartile range IQR. A P-value was regarded as significant at P 0.01.

RESULTS

Table 1 displays the participant's demographic information. There was no difference in age or sex ratio between the MS and control groups. Patients with MS were mostly under the age of 30 years 59.1% while 40.9% were over the age of 30 years **Table1.** Ages ranged from 16 to 41 years for the 22 participants in the MS group, with a mean age of 24.32 7.27 years.

Table 1: Comparison between the two studied groups according to demographic data

Demographic data	Cases (n = 22)	Control (n = 22)	Test of Sig.	P
Sex				
Female	17 (77.3%)	11 (50.0%)	χ^2= 3.536	0.060
Male	5 (22.7%)	11 (50.0%)		
Age (years)				
<30	13 (59.1%)	13 (59.1%)	χ^2= 0.000	1.000
≥30	9 (40.9%)	9 (40.9%)		
Min. – Max.	17.0 – 48.0	10.0 – 68.0		
Mean ± SD.	29.36 ± 9.84	32.14 ± 15.08	t= 0.722	0.474
Median (IQR)	26.0 (25.0 - 43.0)	26.0 (24.0 – 45.0)		

χ^2: **Chi square test** **t: Student t-test** p: p value for comparing between **Cases** and **Control**
*: Statistically significant at p ≤ 0.05 IQR: **Inter quartile range** SD: **Standard deviation**

The majority of the MS patients belonged to the RRMS category with a total of 18 subjects 81.8% while a total of 4 subjects 18.2% met the criteria for the SPMS **Table 2**.

Table 2: Distribution of the studied cases according to different parameters (n = 22)

	No. (%)
MS Phenotype	
RRMS	18 (81.8%)
SPMS	4 (18.2%)
Brain MRI	
Number of T2 lesions	
Min. – Max.	3.0 – 18.0
Mean ± SD.	8.86 ± 3.78
Median (IQR)	8.50 (7.0 – 12.0)
Site(s) of the lesion(s)	
Cortical Juxta cortical	14 (63.6%)
Periventricular	21 (95.5%)
Infratentorial	15 (68.2%)
# of enhanced lesions	
0	20 (90.9%)
2	2 (9.1%)
Min. – Max.	0.0 – 2.0
Mean ± SD.	0.18 ± 0.59
Median (IQR)	0.0 (0.0 – 0.0)

IQR: **Inter quartile range** SD: **Standard deviation**
SPMS: Secondary Progressive Multiple Sclerosis RRMS: Relapsing Remitting Multiple Sclerosis

There was insignificant association between *H. Pylori* IgG and IgM antibodies between the cases and controls **Table 3.**

Table 3: Comparison between the two studied groups according to *H-Pylori* antibosies

H-Pylori.Ab	Cases (n = 22)	Control (n = 22)	Test of Sig.	P
IgG				
Negative <0.75	14 (63.6%)	11 (50%)	χ^2= 0.834	0.361
Positive ≥0.75	8 (36.4%)	11 (50%)		
Min. – Max.	0.12 – 1.50	0.21 – 1.80	U= 207.50	0.418
Mean ± SD.	0.64 ± 0.45	0.71 ± 0.41		
Median (IQR)	0.53 (0.25 – 0.90)	0.74 (0.35 – 0.90)		
IgM				
Negative ≤30	10 (45.5%)	7 (31.8%)	χ^2= 0.863	0.353
Positive >30	12 (54.5%)	15 (68.2%)		
Min. – Max.	2.10 – 43.80	12.40 – 46.80	U= 209.50	0.445
Mean ± SD.	27.51 ± 14.57	32.68 ± 8.26		
Median (IQR)	31.35 (12.6 – 41.2)	32.25 (28.1 – 39.3)		

χ^2: **Chi square test** **U: Mann Whitney test** p: p value for comparing between **Cases** and **Control**

No significant difference between *H. Pylori* IgG antibodies seropositivity and MS variables such as age of onset of the disease, duration of the disease, number of relapses, EDSS, MS phenotype, Number of T2 lesions in univariate analysis model **Table 4**

Table 4: Univariate logistic regression analysis for positivity of IgG regarding to different factors (n = 8 vs. 14)

	IgG		Univariate	
	Negative (n = 14)	**Positive (n = 8)**	**OR (LL – UL 95%C.I)**	**P**
Age at onset	22.79 ± 6.42	27.0 ± 8.32	1.086 (0.957 – 1.233)	0.199
Duration since 1st attack	6.07 ± 5.43	4.0 ± 2.37	0.879 (0.659 – 1.174)	0.383
Duration since diagnosis	4.14 ± 3.96	3.20 ± 1.64	0.908 (0.633 – 1.303)	0.600
Latency	2.82 ± 2.69	2.0 ± 1.41	0.827 (0.438 – 1.559)	0.556
Number of relapses	2.86 ± 1.10	2.0 ± 1.07	0.405 (0.132 – 1.239)	0.113
EDSS	3.0 ± 0.81	2.06 ± 1.05	0.275 (0.075 – 1.009)	0.052
DMT history				
TTT naïve	8 (57.1%)	4 (50%)	1.000	0.746
On DMT	6 (42.9%)	4 (50%)	1.333 (0.233 – 7.626)	
MS Phenotype				
RRMS	11 (78.6%)	7 (87.5%)	1.909 (0.164 – 22.202)	0.605
SPMS	3 (21.4%)	1 (12.5%)	1.000	
Number of T2 lesions	9.79 ± 3.91	7.25 ± 3.15	0.797 (0.587 – 1.081)	0.144
Site(s) of the lesion (s)				
Cortical Juxta cortical	9 (64.3%)	5 (62.5%)	0.926 (0.153 – 5.608)	0.933
Periventricular	14 (100%)	7 (87.5%)	–	1.000
Infratentorial	9 (64.3%)	6 (75%)	1.667 (0.240 – 11.575)	0.605
# of enhanced lesions	0.0 ± 0.0	0.50 ± 0.93	–	0.999

Quantitative data was expressed using no. (Mean ± SD.)
Qualitative data was expressed using Number (%) OR: **Odd`s ratio**
C.I: Confidence interval LL: Lower limit UL: Upper Limit
p: p value for **Odd`s ratio** for comparing between the studied groups
SPMS: Secondary Progressive Multiple Sclerosis RRMS: Relapsing Remitting Multiple Sclerosis
DMT: Disease Modifying therapy EDSS: Expanded Disability Status Scale

There was insignificant difference between *H. pylori* IgM antibodies seropositivity and MS variables i.e. age of onset of the disease, duration of the disease, number of relapses, EDSS, MS phenotype, Number of T2 lesions in univariate analysis model **Table 5.**

Table 5: Univariate logistic regression analysis for positivity of IgM regarding to different factors (n = 12 vs. 10)

	IgM		Univariate	
	Negative (n = 10)	**Positive (n = 12)**	**OR (LL – UL 95%C.I)**	**P**
Age at onset	25.90 ± 7.98	23.0 ± 6.69	0.943 (0.834 – 1.067)	0.351
Duration since 1st attack	7.78 ± 5.95	3.55 ± 2.38	0.737 (0.517 – 1.052)	0.093
Number of relapses	2.80 ± 1.48	2.33 ± 0.78	0.681 (0.309 – 1.499)	0.340
EDSS	3.0 ± 1.22	2.38 ± 0.68	0.485 (0.181 – 1.301)	0.150
MS Phenotype				
RRMS	7 (70%)	11 (91.7%)	4.714 (0.405 – 54.826)	0.215
SPMS	3 (30%)	1 (8.3%)	1.000	
Number of T2 lesions	10.30 ± 4.52	7.67 ± 2.67	0.805 (0.613 – 1.058)	0.120
Site(s) of the lesion (s)				
Cortical Juxta cortical	5 (50%)	9 (75%)	3.000 (0.495 – 18.169)	0.232
Periventricular	9 (90%)	12 (100%)	–	1.000
Infratentorial	8 (80%)	7 (58.3%)	0.350 (0.051 – 2.407)	0.286
# of enhanced lesions	0.20 ± 0.63	0.17 ± 0.58	0.905 (0.211 – 3.872)	0.892

Quantitative data was expressed using no. (Mean ± SD.)
Qualitative data was expressed using Number (%) OR: **Odd`s ratio**
C.I: Confidence interval LL: Lower limit UL: Upper Limit
p: p value for **Odd`s ratio** for comparing between the studied groups

DISCUSSION

Studies show that environmental, genetic and epigenetic factors play a causal role in MS [16].

Many researches have revealed a negative correlation between *H. pylori* serology and MS, which implies that *H. pylori* infection may possibly provide protection against MS. But the precise mechanism through which this protective effect manifests itself is still poorly known[17]. Yao's group performed a meta-analysis that included 1553 MS patients from 9 distinct papers that were all case-control studies that used various diagnostic techniques to identify *H. pylori* infection, including ELISA, western blot, immunofluorescence, and latex agglutination. The investigators found no statistically significant differences in the diagnostic methods, and the prevalence of *H. pylori* infection was lower in MS patients than in healthy persons. Their study demonstrates a poor association between MS and *H. pylori* infection, particularly in western countries. Prospective trials are required to evaluate whether *H. pylori* infection serves as a protective factor to the development of MS. On the other hand, it has been proposed that active *H. pylori* infection may contribute to the pathogenesis of autoimmune illnesses such Guillain-Barré syndrome, autoimmune pancreatitis, and autoimmune mucosal atrophy[19] and that it may play a role in the onset of MS [18].

Several non-invasive tests can identify *H. pylori* infection with excellent sensitivity and specificity. The 13^C urea breath test UBT, stool antigen tests SAT, and serological tests for IgG anti-*H. pylori* antibodies [20].

IgG antibody testing doesn't distinguish between active and past infections and are hence ineffective for assessing the efficacy of eradication therapy. All tests have significant limits in some patient populations. A confirmatory test is recommended in populations where *H. pylori* prevalence is low due to the possibility of false-positive results [21].

IgG H-pylori seropositivity in MS was observed to be considerably lower in the current study 36.4% as compared to healthy controls 50%. This is consistent with a study from 2013 by Long and colleagues. Wherein Chinese MS patients likewise showed a negligible correlation[22].

In our study, the univariate model found no significant correlation between EDSS scores and *H. pylori* Abs IgG and IgM. In contrast to research by Makristathis and coworkers[23], which found a significant difference in EDSS scores between seropositive and seronegative people. By examining IgG and IgM antibodies in blood samples, investigators found a substantial correlation between *H. pylori* and MS, drawing the conclusion that the infection may act as a preventative measure against MS.

Data from Egypt show that a high anti-*H. pylori* heat shock protein hsp 60 IgG level is correlated with MS and can be used as a biomarker for progression of patients with MS, where the prevalence of *H. pylori* disease appears to be very high overall seropositivity rate of 91.7% in Egyptian rural population, indicating a potential link between *H. pylori* infection and the pathogenesis of MS particularly SPMS phenotype [24]. In the current study SPMS phenotype represented 18.2% of all cases where there was no significant difference between *H. Pylori* IgG antibodies seropositivity and SPMS phenotype. This finding requests for more large-scale, well-designed research to investigate the link between active *H. pylori* infection and MS.

At a 2-year follow-up study, Clinically Isolated Syndrome CIS phenotype patients with effective *H. pylori* eradication had a significantly lower second episode, which was associated with improved mean EDSS, indicating a potential role for this infection in the development of CIS and/or progression to clinically definite MS and its progression [25]. In our study 45.5% of patients reported a second episode; however CIS phenotype was not represented in our groups.

Cantero-Fortiz and colleagues[26], reported a considerably higher quantity of *H-pylori* IgG in SPMS phenotype than in RRMS phenotype; however, they found no significant connection between seropositivity or concentration of IgG against HP and the inflammatory phenotype of MS, age, length of disease, or EDSS. In the current study we reported the opposite results as *H-pylori* IgG increased in RRMS phenotype than SPMS phenotype. The specific pathogenic mechanism is still unknown; however these findings could imply that low *H. pylori* exposure in people prone to MS could drive the start and clinical duration of the condition.

In our study, we used a healthy control group; avoiding the limitation of previous studies such as Kountouras and colleagues[27] where authors allocated iron deficient anemia IDA patients to the control group; IDA patients were expected to have a high prevalence of H-pylori and the control group was claimed to be "inconvenient" thereafter [27]. Additionally, both IgM and IgG antibodies were analyzed to reflect the effect of both recent and previous *H. pylori* infection, respectively.

Age, gender, ethnicity, and lifestyle factors, which may affect both the risk of MS and the chance of *H. pylori* infection, were not examined for in this study and their potential confounding effects. Moreover, serological analysis of *H. pylori* infection is also associated with inadequate specificity, resulting in a high false-positive rate and low accuracy[28].

CONCLUSION

In this study we presented two MS phenotypes and showed that there was no significant correlation observed between *H. pylori* IgG antibodies positivity and various MS variables, such as the age of onset of the disease began, time since the first attack, number of relapses, EDSS score, MS phenotype, and number of T2 lesions, as determined by the univariate analysis model. Understanding the significance of *H. pylori* infection in MS and its potential as a preventive factor against the risk of developing MS requires more research.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authorship:

All authors have made substantial equal contributions to this work

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