REVIEW

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Association between multiple sclerosis and *Helicobacter pylori* in the acute and chronic phases of infection: A systematic review and meta-analysis

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ABSTRACT

Multiple sclerosis is a demyelinating autoimmune disease in the central nervous system. It is associated with several factors, one of which is *Helicobacter pylori.* We suggested that HP may have different effects on MS in the acute and chronic phases; therefore, we evaluated the HP and MS association in acute and chronic phases of infection. Scopus, PubMed, and Web of Science databases were used for systematic search. Finally, according to the inclusion criteria, eight studies were selected. According to the result of this study, there was no significant difference in the disease duration and EDSS between MS with HP. Pooled results showed that the standard difference in the mean EDSS was - 0.910, and the standard difference in the mean duration was - 0.067. Also, by comparing antibody levels in the acute and chronic phases of HP with the control group. Finally, we evaluate the mean EDSS between the two phases of infection, which shows that the mean EDSS and the clinical weaknesses of MS in the acute phase were slightly higher than in the chronic. In conclusion, HP infection can have a stimulating or inhibiting effect on the immune system based on the onset and activity of the infection.

Keywords: multiple sclerosis, *Helicobacter pylori,* antibody, EDSS, acute infection

INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system [1,2]. MS is a juvenile's most common central nervous system demyelinating disease [3]. Genetic and environmental factors can affect the progression of MS by activating T lymphocytes and inflammatory factors [4]. Studies have reported that the balance between anti-inflammatory and pro-inflammatory agents such as Th1, Th17, and T reg cells in terms of count or activity can play an essential role in the development of MS [5,6].

Helicobacter pylori (HP*)* is a gram-negative, microaerophilic bacteria that colonizes the stomach and duodenum of more than half of the world's population [7,8]. Although most HP-infected patients are asymptomatic, about 10-15% develop symptomatic diseases such as gastric or duodenal ulcers and gastric cancer [5,9]. Childhood HP or chronic HP infection can act paradoxically as a protective factor in atopic diseases under certain conditions. HP infection, besides gastrointestinal disease, may lead to extraintestinal disorders such as Alzheimer's disease, Parkinson's disease, seizure, and MS [10-12].

The gut microbiota is a collection of microorganisms that colonize the gastrointestinal tract and impress the host immune system [13]. The gut microbiome can affect the brain, the gut-brain axis, which is described as a physiological network connection between the brain and the gastrointestinal tract. Gut-microbiome balances the levels of anti-inflammatory and pro-inflammatory cytokines and other metabolites, regulating brain function [14]. In this regard, this proposition has been recently raised that microorganisms may cause MS [15].

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Various environmental factors may affect the course of MS, in which case, infection is one of the critical factors that affect the host's response to the MS disease [16]. Based on the result of studies so far, the association between HP and MS is controversial. Several studies have reported negative correlations, others have reported positive ones, and fewer studies have showed no correlation between MS and HP [17-19]. To answer this contradiction, patients with HP infection can get divided into acute and chronic phases of HP infection based on the activity, duration of the infection, and anti-HP antibody level. Considering the results of various studies, three experimental factors, including antibodies, cytokines, and *Helicobacter pylori* specific heat shock protein (HP-HSP] levels, can be suitable criteria for differentiating acute and chronic phases of infection [20,21], which examined the antibody level in this study. Because of dividing the HP course into two phases, we studied the clinical characteristics of MS in both groups.

Therefore, this systematic review aimed to compare the anti-HP IgG level and MS clinical course in co-infection with HP patients between the acute and chronic phases of HP infection to evaluate the mentioned proposal.

METHOD

Search strategy

This systematic review and meta-analysis were performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This systematic search was conducted using Scopus, PubMed, and Web of Science electronic databases. The following search terms were used ("Multiple Sclerosis" OR "MS (Multiple Sclerosis)" OR "Sclerosis, Multiple" OR "Sclerosis, disseminated" OR "Disseminated Sclerosis") AND ("*Helicobacter pylor*i" OR "*H. pylori*" OR "*Campylobacter pylori*" OR "*Helicobacter nemestrinae*"). The search included only English publications between 2006 and 2022. Endnote software was used as a citation manager to save articles. To select studies based on inclusion criteria, we reviewed the search results' titles, abstracts, and full text. Inclusion criteria in this study were: 1. observational studies, including case-control design. 2. MS was diagnosed according to accepted international criteria (for example, McDonald, Poser, or Schumacher) 3. Publications describing the association between *Helicobacter pylori* and Multiple sclerosis. 4. Studies were describing the levels of anti-HP antibodies in MS patients. The review articles, case reports, case series, and animal studies were excluded.

Quality assessment and data extraction

Using the nine-point Joanna Briggs Institute critical appraisal checklist for studies, two researchers conducted the quality assessment, and disagreements were resolved by consensus. The included studies met more than half of the quality assessment parameters. Studies were selected based on inclusion criteria, and then the following data were extracted: author name, design of the study, country, publication year, number of case and control samples, MS prevalence in HP-seropositive and seronegative, Expanded Disability Status Scale (EDSS), anti-HP IgG level, and duration of MS disease. McDonald criteria diagnosed MS, and a blood sample and ELISA reader detected the antibody level. The extracted information included the journal name, publication year, language, country of study, count of all articles and each type of study, study design, research question, the device used, patient demographics, and statistical analysis methods.

Statistical analysis

The statistical analysis and construction of graphs were performed with a comprehensive meta-analysis (CMA) version 3 (Biostat Inc., Englewood, NJ) with a random effect model plotted on forest plots. The pooled standard difference in mean with 95% CI gave the summary estimate. *I-square* (I^2) test was used for heterogeneity. The funnel plot was used to assess visual bias, as confirmed by Egger's regression test ($p < 0.05$ was considered a statistically significant publication bias).

RESULT

Identification of eligible studies

Based on the keyword of this study, we identified about 424 articles from Scopus, PubMed, and Web of Science. After removing review and duplicate studies, we selected eight publications after reading the titles and abstracts based on the inclusion criteria (Figure 1).

Study characteristics

All eight selected studies are presented in Table 1. Articles published between 2007 and 2022. These studies had seven case-control designs and one retrospective design. The source of studies is three studies from Greece, three studies from Iran, one study from Mexico, and one study from Japan.

Overall effects and subgroup analysis

In the first step, we compared the MS characteristic between MS with HP-seropositive and seronegative. EDSS and disease duration were compared between the two groups. Pooled results showed std difference in the mean EDSS was - 0.910 (95% CI: - 2.83, 1.01, *P-value* = 0.354) and std difference in the mean duration was - 0.067 (95% CI: - 0.31, 0.17, *P-val-*

TABLE 1. Characteristics of studies

Study	Design	Country	Mean Age (year)	Anti-HP IgG in MS (RU/ml)	EDSS in HP+ infection (number)	Duration in HP+ infection (year)	References
Afiati Salim 2017	Case-control	Iran	33.3	62	NA	NA	(20)
Efthymiou 2016	Case-control	Greece	45.6	131.87	NA	NA	(21)
Li 2006	Case-control	Japan	36.7	NA	3.8	12.2	(24)
Gavalas 2007	Retrospective	Greece	38.6	48.8	NA	NA	(36)
Kiani 2020	Case-control	Iran	36.8	43.37	NA	NA	(37)
Ranjbar 2019	Case-control	Iran	31.8	19	2	4.7	(38)
Gerges 2018	Case-control	Greece	26.9	NA	4.5	14.5	(39)
Cantero 2022	Case-control	Mexico	42.3	19	3.6	8.4	(40)

HP: *Helicobacter Pylori;* NA: not available

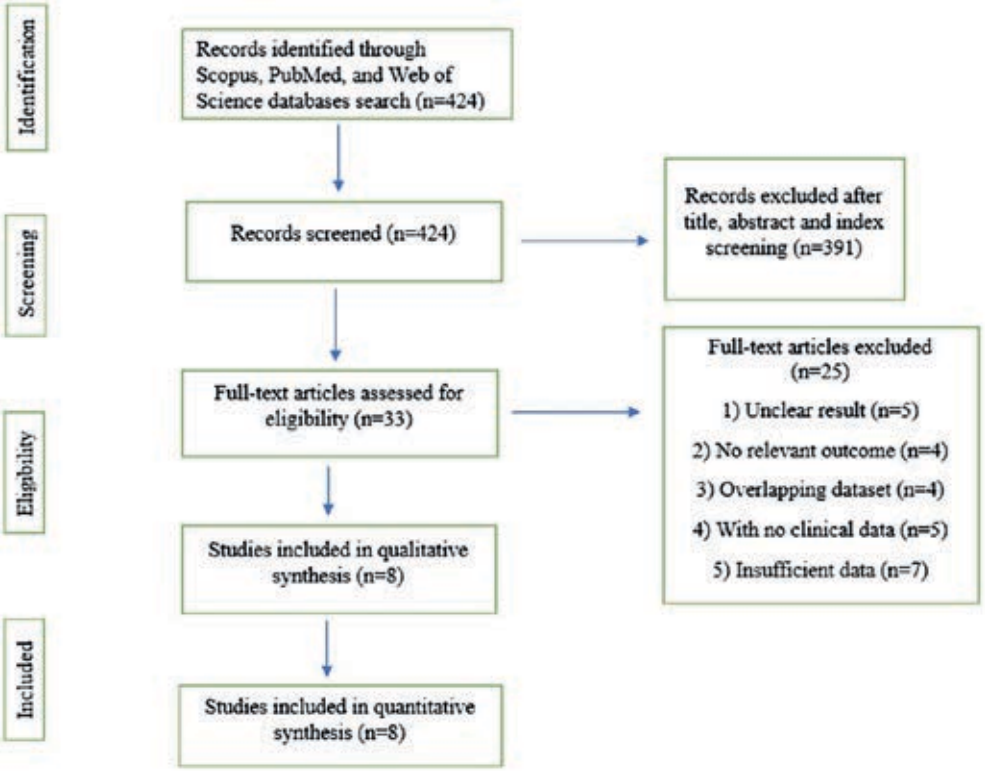
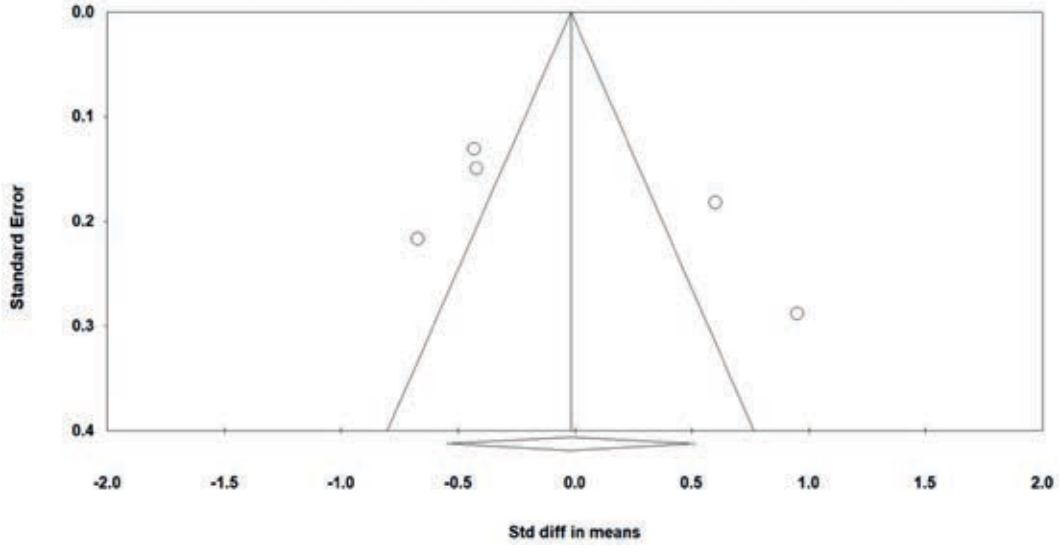


FIGURE 1. Prisma flow chart of study selection



SUPPLEMENTARY FIGURE 1. Funnel plot comparing acute and chronic HP IgG levels with the control group

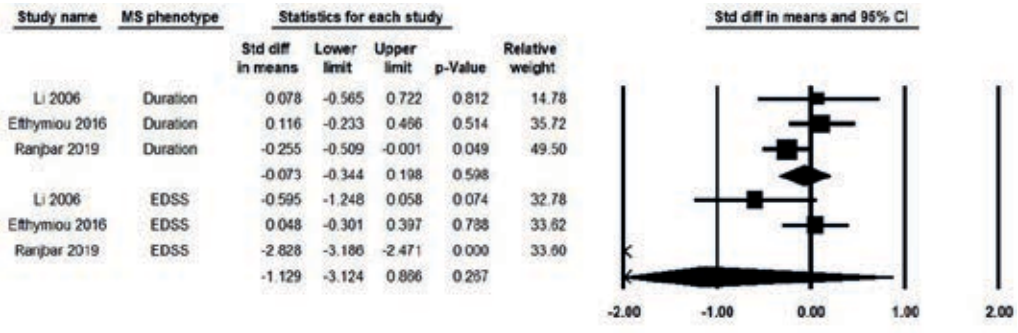
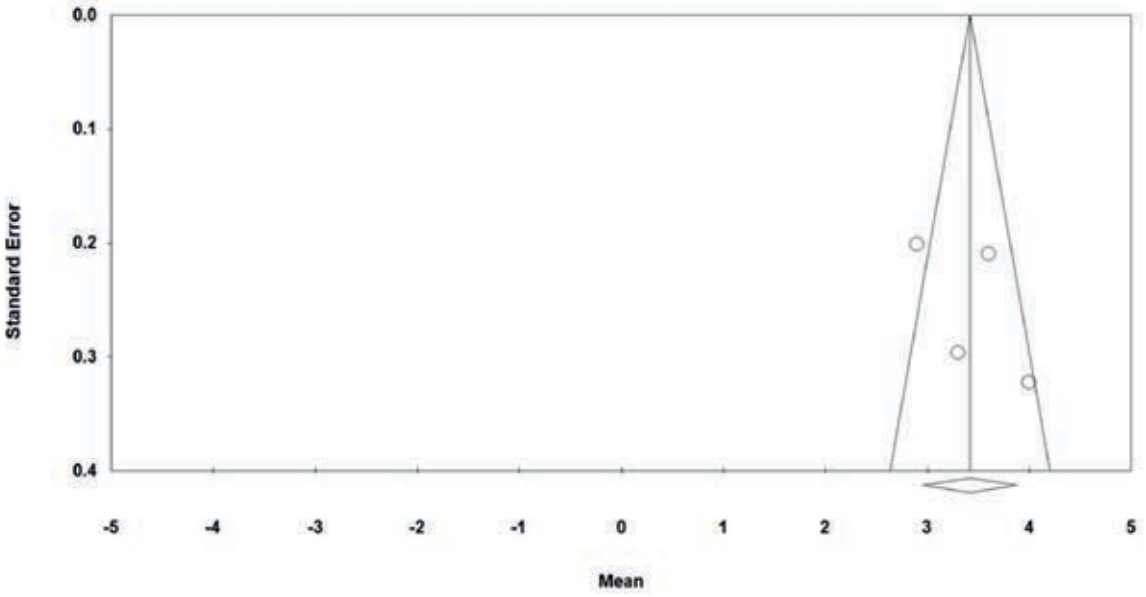


FIGURE 2. Comparing clinical characteristics of HP-positive and HP-negative MS patients
Favours A: HP-positive Favours B: HP- negative



SUPPLEMENTARY FIGURE 2. Funnel plot of EDSS mean in acute and chronic groups

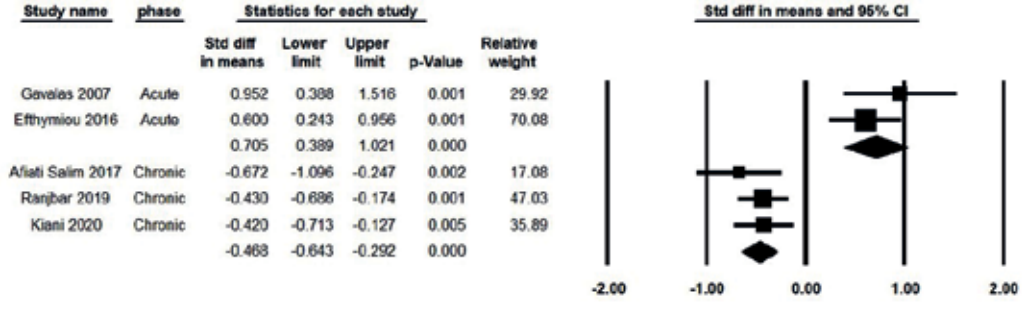


FIGURE 3. Comparing acute and chronic HP IgG levels with the control group
Favours A: Control Favours B: MS patients

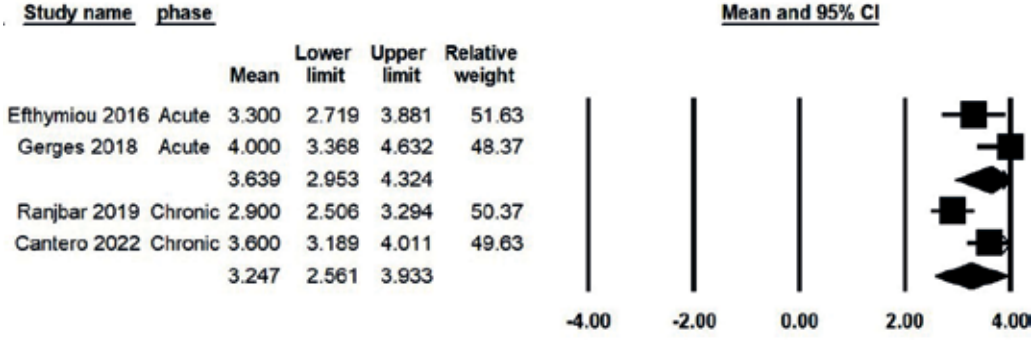


FIGURE 4. Forest plot of EDSS mean in acute and chronic groups

ue = 0.592) (Figure 2). There was no significant difference in EDSS and disease duration between HP-seropositive and seronegative.

We divided MS with HP-seropositive into acute and chronic phase of HP infection in the second step. We also compared anti-Hp IgG levels in the acute and chronic phases of HP between MS disease and the control group. The std difference in anti-Hp IgG mean was 0.705 (95% CI: 038, 1.02, *P-value*<0.001) in acute and - 0.468 (95% CI: - 0.64, - 0.29, *P-value* <0.001) in chronic phases, according to the pooled results (Figure 3). As far as the result of these studies is concerned, there was a significant difference in antibody levels between MS and control groups in both acute and chronic phases.

As a third step, we also evaluate EDSS in the acute and chronic phases of HP in MS patients (Figure 4). Based on the pooled result of this study, the mean EDSS in acute and chronic groups was 3.63 (95% CI: 2.95, 4.32) and 3.24 (95% CI: 2.56, 3.93), respectively. The results showed that the mean EDSS in the acute phase is slightly higher than in the chronic phase. The difference in EDSS between acute and chronic phases needs further investigation in future studies.

Publication bias

Funnel plots were used for visual bias. A funnel plot of antibody comparison indicates poor asymmetry, but Egger's test rejects it. The two other funnel plots are symmetrical. The Egger test showed no significant evidence of publication bias in this meta-analysis (Table 2). Additionally, we have attached the funnel plots as supplementary Figure 1,2.

DISCUSSION

MS is a chronic inflammatory disease linked to genetic and environmental factors. The presence of bacterial and viral infections can act as a risk or protective factor in MS [2]. In the current meta-analysis, we want to examine HP infection's positive or negative effects on MS disease. Some previous studies have suggested that HP infection may be beneficial in MS disease, while some others have reported the opposite [20,21]. Although there are few studies on the relationship between MS and HP, some factors can answer this controversial issue [22].

We first compared the clinical characteristics of MS patients in HP-seropositive and seronegative ones. Basically, we want to evaluate the HP infection effect on MS. There are controversial reports about the relationship between HP and MS. According to other studies, this association may be a positive or a negative impact, or it may be neutral [20,21,23]. In a Japanese study, Li et al. reported an inverse association between HP-seropositivity and EDSS score, suggesting a protective effect [24]. Gavalas et al. state that HP infection appears to be more frequent in MS patients; therefore, HP can be a risk factor for developing MS [18]. Thus, we adjusted the data by age and sex, and based on the results of this meta-analysis, we compared EDSS and the disease duration between HP-positive and HP-negative. As a result, we did not find any significant relationship between them. However, this situation can be challenged. For example, Pedrini et al. divided MS patients with and without HP into male and female groups and showed that EDSS is significantly lower in Hp-seropositive females than the HP-seronegative ones [19]. In this study, we divided HP-seropositivity into acute and chronic phases of HP infection and suggested that HP may have a different effect on MS in the acute and chronic phases.

Based on the results of this study, we investigated the acute and chronic phases of HP in MS disease. According to previous information, acute and chronic phases of HP have differences in terms of onset and duration, clinical symptoms, and laboratory aspects. The acute phase begins right after the infection manifestation in the tissue samples; And 74 days, the chronic phase begins. Also, acute H pylori infection may be characterized by specific upper gastrointestinal symptoms in adults [particularly men) [25, 26], including epigastric burning, distention or bloating, belching, episodic nausea, flatulence, and halitosis. There is a less clear association between dyspeptic symptoms and chronic infection. Also, most of the infected patients are asymptomatic. HP infection phases are also different in terms of serology. IgM and IgA antibodies appear on days 14-74. IgG joins them on days 70-140; And then IgA disappears on days 140-190. After that, IgM is gone [27,28]. Initial HP infection causes an acute reaction of the innate immune system and polymorphonu-

TABLE 2. The complete results of heterogeneity and publication bias examination

Variable	Number of report/s	Standard error	95% CI		Heterogeneity			Egger's regression	
			Lower limit	Upper limit	X^2	*p*-value	I^2	*P*-value	*t*-value
Mean of EDSS and duration in HP+ and HP-	6	0.07	-1.54	0.38	189.687	<0.001	97.364	0.95	0.06 6
IgG levels in acute and chronic	5	0.271	-0.551	0.513	45.2	<0.001	91.154	0.312	1.211
Mean EDSS in acute and chronic	4	0.235	2.95	3.86	10.533	0.015	71.518	0.423	0.997

clear (PMN). Also, in this phase, reactive oxygen is produced, which can affect the DNA structure and the immune system's function [29]. We can witness CD4+ and PMN infiltration during this phase. In the chronic phase, as opposed to the acute, fewer symptoms exist, and these symptoms may persist throughout the host's life [30].

There is an association between MS and HP called molecular mimicry. HP infection antigens may induce cross-reactivity with oligodendrocytes ganglioside surface components in the central nervous system (CNS), activate the humoral and cellular immune system, and contribute to CNS damage [31]. Studies on mice showed a beneficial effect of HP infection on the clinical symptoms of MS. The protective role of infection is probably related to the inhibition of Th1 and Th17 responses [32]. The proposed protective mechanism by H. pylori infection in EAE and MS involves restoring the balance between Th1, Th17, and Treg lymphocytes subsets via several pathways, specifically through those connected to IL-10 functions and CCR6–CCL20 interaction [33]. HP infection in its chronic period, which often remains from childhood, leads to a shift towards T-regs and prevents the sensitization of the immune system. While in acute infection, the immediate stimulation of the immune system and molecular mimicry can bring about the intensification of the immune response. Therefore, the duration of the infection and its phase can be important [34]. This study shows that in the acute phase, the concentration of anti-HP IgG in the MS group is significantly higher than in the control group, and in the chronic phase is significantly lower than the control group, but this will require further study in the future. As mentioned, the antibody concentrations in the acute and chronic phases of HP in MS patients are respectively higher and lower compared to the control group. Low antibody levels in the chronic phase may result from bacterial load reduction or immunosuppressive medications administration by MS patients.

At the end of this study, the MS phenotype was compared between the acute and chronic phases of HP. So far, we have analyzed that the mean EDSS in the acute phase is slightly higher than in the chronic phase, indicating that acute HP infection was involved in CNS damage. The protective role of HP in chronic infection and the harmful role in acute infection support the hypothesis that the immune system may be boosted at the onset of infection and suppressed over time [35]. More clinical and experimental studies are needed to evaluate the effects of HP on the development of MS.

According to the extracted data in this study, we first compared the clinical characteristic of MS with HP-seropositive and seronegative, but did not observe a significant difference between the two groups. Therefore, at this level, we cannot get to a proper conclusion regarding the relationship between MS and HP. Consequently, we separated two different phases of the infection based on clinical symptoms, antibody level, and duration of the infection and investigated the relationship between MS and HP in acute and chronic phases. The comparison of the characteristics of MS in acute and chronic infections showed that the average EDSS in the acute phase is slightly higher than in the chronic phase. Also, the clinical weaknesses (especially functional) of MS patients in the acute phase are slightly more severe than in the chronic phase, so it is possible that examining the relationship between MS and HP in the two clinical phases of the infection can provide more accurate information, but this requires further study.

In summary, HP infection can have a stimulating or inhibiting effect on the immune system based on the onset and activity of the infection; hence, it may have a positive or negative impact on the course of MS. So, we hypothesize that HP infection may have a dangerous effect on MS in the acute phase, but the chronic phase plays a protective role during MS disease based on its immunomodulatory effect.

Limitations

Non-English language articles.

A tiny number of articles are related to antibody levels.

Conflict of interest: none declared
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