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Review Article

Helicobacter pylori infection and demyelinating disease of the central nervous system

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ABSTRACT

Helicobacter pylori (*H. pylori*) colonize > 50% of the entire human population. Generally, *H. pylori* infect the human stomach in infancy when parietal cells secreting gastric acids, which reduce the survival of *H. pylori*, are not well matured. Once acquired, the bacterium persists for life. Thus, *H. pylori* infection reflects sanitary conditions during childhood. > 10 studies performed in various Eastern and Western countries as well as two meta-analyses collectively indicated the *H. pylori* infection rate is significantly lower in patients with multiple sclerosis (MS) than in healthy controls. Thus, the bacterium might be a protective factor for MS, especially in low prevalence countries and younger generations that grew up in the low prevalence era. The protective effects of *H. pylori* might be explained by the hygiene hypothesis—encountering generic infection early in life facilitates development of the immunoregulatory system, which suppresses overactivity of autoimmune T cells later in life. However, no influence of common childhood infections on MS risk was reported by large MS cohort studies. Direct attenuation of autoreactive Th1 and Th17 cells by *H. pylori* infection was found in experimental autoimmune encephalomyelitis, an animal model of MS. These observations may underscore the direct protective effects of *H. pylori* on MS rather than generic infection in childhood. By contrast, several studies reported that *H. pylori* infection rates are significantly higher in anti-aquaporin-4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD) than in healthy controls. *H. pylori* strongly activate Th17 cells via the induction of IL-23, resulting in neutrophil mobilization and activation. *H. pylori* neutrophil-activating protein (NAP) is a major proinflammatory protein responsible for the pathology of *H. pylori*-related gastric inflammatory diseases. Anti-*H. pylori*-NAP antibody levels were positively correlated with final EDSS scores and myeloperoxidase levels in anti-AQP4 antibody-positive NMOSD patients. Given that spinal cord lesions of NMOSD are heavily infiltrated with myeloperoxidase-positive neutrophils, *H. pylori*-NAP, which can be absorbed and presented to the host immune system, may exacerbate NMOSD. Thus, *H. pylori* infection and its proinflammatory proteins, such as NAP, may contribute to the pathology of anti-AQP4 antibody-related neural damage, by activating neutrophils. It is interesting that two representative demyelinating diseases of the central nervous system are differentially modulated by chronic *H. pylori* infection. The direct effects of *H. pylori* infection on MS and NMOSD warrant future studies.

1. *Helicobacter pylori* infection and its relation to gastric and extra-gastric disorders

Helicobacter pylori (*H. pylori*) are a spiral, flagellated, Gram-negative microaerophilic bacterium that selectively colonize the human stomach (Atherton, 2006; Blaser, 1993). > 50% of the entire human population is infected with *H. pylori* (Blaser, 1993), which belongs to the phylum *Proteobacteria*, class *Epsilonproteobacteria*, order *Campylobacterales*, family *Helicobacteraceae*, genus *Helicobacter*. *H. pylori* infection is thought to mainly occur before 2 years of age, primarily because the parietal cells that secrete gastric acids, which reduce the survival of *H. pylori*, are not well matured during infancy (Graham, 1991). Once acquired, the bacterium persists for life (Graham, 1991). Thus, a difference in the frequency of *H. pylori* infection suggests a distinction in the infectious environment during childhood. Indeed, in Japanese, the prevalence of *H. pylori* infection is lower in the population born after 1950 than in those born before 1950, reflecting improved sanitation after World War II (Asaka et al., 1992).

Most individuals persistently colonized with *H. pylori* are asymptomatic while approximately 10% to 15% develop symptomatic

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gastroduodenal disease (Atherton, 2006). Persistent infection of *H. pylori* is associated with chronic gastritis, peptic ulcer, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma (Atherton, 2006; Salama et al., 2013; Pereira and Medeiros, 2014). *H. pylori* can be eradicated by combined therapy of proton pump inhibitor and antibiotics, such as amoxicillin hydrate, and clarithromycin. Eradication of *H. pylori* has been reported to decrease the incidence of gastric cancer (Ford et al., 2015; Lee et al., 2016). In addition, *H. pylori* infection is thought to be associated with extra-gastric disorders. The most well-known example is idiopathic thrombocytopenic purpura (ITP), in which autoantibodies against platelet glycoproteins, such as GPIIb-IIIa, and GPIb-IX, play a key role in destroying platelets (McMillan et al., 1987; Kiefel et al., 1991; Tomiyama and Kosugi, 2005). Over 70% of older adult Japanese ITP patients are infected with *H. pylori* (Fujimura et al., 2005). Successful eradication of *H. pylori* results in a significant increase in platelet counts in approximately 60% of *H. pylori*-positive ITP patients, together with the disappearance of anti-platelet antibodies (Gasbarrini et al., 1998). Although the evidence is weak, the positive association of *H. pylori* with other autoimmune diseases, such as autoimmune atrophic thyroiditis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and Sjögren syndrome, has been suggested (de Luis et al., 1998; Zentilin et al., 1999; Hasni, 2012).

2. *Helicobacter pylori* infection and multiple sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). Autoimmunity against CNS antigens is hypothesized to be involved in its pathogenesis, but this has not been proven. MS is thought to be caused by a complex interplay between genetic and environmental factors (Ebers, 2008). In 2007, we reported the first study to show a negative association of *H. pylori* infection with multiple sclerosis (MS) in Japanese (Li et al., 2007) and proposed *H. pylori*.as a protective factor for MS. In this study, the *H. pylori* seropositivity rate was significantly lower in MS patients (n = 53) than in healthy controls (n = 85) (22.6% vs. 42.4%). Logistic regression analysis revealed that *H. pylori* infection had a significant negative association with MS (OR = 0.29), even though birth year was used as a variable (Li et al., 2007). Moreover, *H. pylori* infection demonstrated a significant inverse association with EDSS score (OR = 0.61) and fulfillment of McDonald MRI criteria for space (OR = 0.11) (Li et al., 2007), suggesting *H. pylori*. Infection is a protective factor against the development of MS-like brain lesions and subsequent disability.

Thereafter, Mohebi et al. also reported that *H. pylori* seropositivity rates were significantly lower in MS patients (n = 163) than in healthy controls (n = 150) (54% vs. 73%) in the Iranian population, and that EDSS scores were also significantly lower in *H. pylori* seropositive MS patients than seronegative patients (Mohebi et al., 2013). Malli et al. reported an inverse relationship of *H. pylori* infection with MS in the Indian population (MS patients, n = 139, 22.5% vs. controls, n = 139, 46%; OR = 0.319), using approximately a 1:1 ratio of relapsing remitting MS (RRMS) and secondary progressive MS (SPMS) patients (Malli et al., 2015). Salim et al. also observed significantly lower seropositivity rates for *H. pylori* in Iranian patients with RRMS (n = 45) than in healthy controls (n = 45) (Salim et al., 2017). These results are consistent with the findings in Japanese MS patients.

Regarding Caucasian MS patients, the study of an Australian MS cohort by Pedrini et al., reported that *H. pylori* seropositivity was significantly lower in MS patients (n = 550) than in controls (n = 299) (16% vs. 21%) (Pedrini et al., 2015). The significant decrease in *H. pylori* seropositivity rate was observed in females (14% vs. 22%) but not males (19% vs. 20%). Interestingly, when adjusted for age at onset, year of birth, and disease duration, *H. pylori* seropositive female MS patients presented with a significantly lower EDSS score compared with seronegative female patients. Although why the protective mechanism of *H. pylori* was observed only in females remains unclear, it might explain the recent increase in the female-to-male ratio of MS in developed countries. Overall, the protective effects of *H. pylori* on MS have been observed among races with distinct prevalence rates of *H. pylori* infection in general populations. Further studies are required to determine whether such influences might differ by sex in certain races.

However, in the Chinese population, the frequency of *H. pylori* seropositivity did not differ significantly between MS patients (n = 42) and healthy controls (n = 27) (73.8% vs. 59.3%) (Long et al., 2013). In Greece, a significantly higher *H. pylori* seropositivity rate was reported in MS patients (n = 29) compared with anemic controls (n = 25) (37.9% vs. 13.1%) (Gavalas et al., 2007). These two studies used a very small number of controls for a prevalence study and the latter study used anemic controls instead of healthy controls. Therefore, selection bias might be inevitable with such a small number of control subjects. In a large-scale study performed in Greece, *H. pylori* seropositivity rates were 50% to 60% (Apostolopoulos et al., 2002). *H. pylori* infection rates might alter according to sanitary conditions in childhood, which vary dependent upon modernization. Thus, a large number of healthy controls adjusted to the birth year are needed to produce scientifically meaningful conclusions.

Two recent meta-analyses have shown that *H. pylori* infection is negatively associated with MS (Jaruvongvanich et al., 2016; Yao et al., 2016). Jaruvongvanich et al. included six studies and found statistically significant lower odds of *H. pylori* infection in MS compared with controls (OR = 0.59, 95%CI = 0.37–0.94) (Jaruvongvanich et al., 2016). Yao et al. reported a meta-analysis of three Western country studies and six Eastern country studies and concluded that the prevalence of *H. pylori* infection was significantly lower in MS patients (n = 1553) than controls (n = 1253) (24.66% vs. 31.84%, OR = 0.69, 95%CI = 0.57–0.83, P < 0.0001) (Yao et al., 2016). The negative association of *H. pylori* infection with MS was statistically significant in Western countries (11.90% vs. 16.08%, OR = 0.63, 95%CI = 0.43–0.91, P = .01) but not in Eastern countries (39.39% vs. 43.82%, OR = 0.79, 95%CI = 0.55–1.14, P = .20). However, these results should be taken with caution because of the racial difference regarding the protective effects of *H. pylori* on MS. For example, the latter meta-analysis contained opticospinal MS cases, an equivalent of neuromyelitis optica spectrum disorders (NMOSD), and NMOSD are relatively common in Eastern countries. As mentioned below, NMOSD has a higher frequency of *H. pylori* infection (Li et al., 2009). Therefore, in Eastern studies, NMOSD cases should be carefully excluded in these association studies.

Overall, the prevalence of *H. pylori* infection is lower in MS than in controls, probably regardless of race, while such protective effects appear to be more evident in countries with a lower prevalence of *H. pylori* infection. Moreover, as previously mentioned, *H. pylori* infection rates sharply decreased in the Japanese population after 1950 (Asaka et al., 1992). It was also noted that MS patients born after 1965 demonstrated a sharp decrease of *H. pylori* infection rates (see Fig. 1) (Yoshimura et al., 2012; Yoshimura et al., 2013; Yoshimura et al., 2014). Thus, in Eastern countries, such protective effects of *H. pylori* may become clearer after sanitation is improved. Decreased *H. pylori* infection in the younger generation may explain in part the increase of MS prevalence by westernization in Eastern countries after World War II (Osoegawa et al., 2009; Kira, 2012; Kira, 2013).

3. *Helicobacter pylori* infection and neuromyelitis optica spectrum disorders

NMOSD is an inflammatory disease of the CNS that selectively affects the optic nerves and spinal cord with characteristic longitudinally extensive spinal cord lesions (LESCLs) extending over three or more vertebral segments. The nosological position of NMOSD has long been a matter of debate. However, the discovery of an IgG specific for NMO, initially designated NMO-IgG but now known as anti-aquaporin-4 (AQP4) antibody, suggested that NMO is a distinct disease entity with a

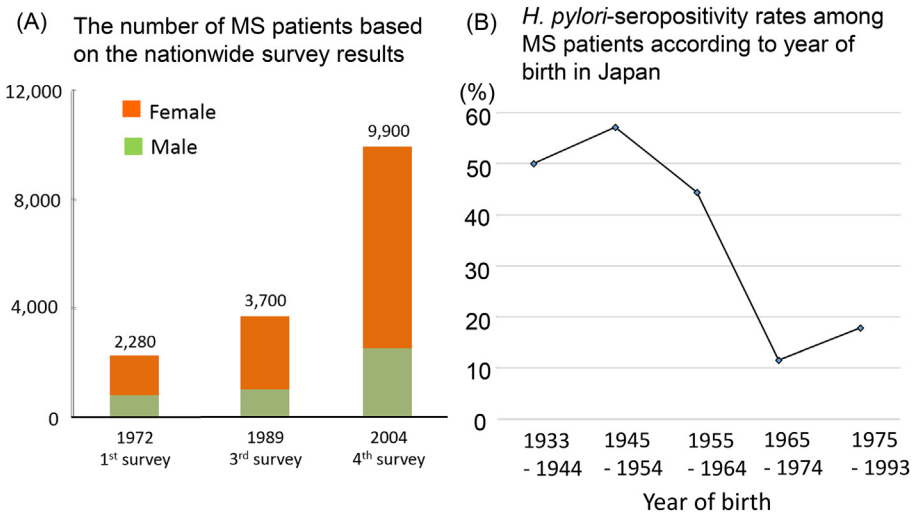

Fig. 1. Increase of MS patients and decrease of *Helicobacter pylori* seropositivity rates in MS patients by year of birth in Japan.
(A) The number of MS patients based on the 1st, 2nd, and 3rd nationwide survey results. The repeated nationwide surveys of MS in Japan show a steady increase of MS patients, especially female patients (Osoegawa et al., 2009). (B) *H. pylori* seropositivity rates among MS patients according to year of birth in Japan. Among MS patients, the proportion of patients with *H. pylori* was markedly decreased in those born after 1965 (Yoshimura et al., 2014). MS, multiple sclerosis.

fundamentally different etiology from MS (Lennon et al., 2004; Lennon et al., 2005). The classification of NMOSD has recently been expanded and new diagnostic criteria have been proposed (Wingerchuk et al., 2015).

Only a few studies have investigated the relationship between *H. pylori* infection and NMOSD. We reported that patients with opticospinal MS, which is now regarded as a part of NMOSD, had a significantly higher frequency of *H. pylori* infection compared with conventional MS patients (Li et al., 2007). In a later study that incorporated an anti-AQP4 antibody assay, Li et al. also revealed that *H. pylori* seropositivity rates were significantly higher in anti-AQP4 antibody-positive NMOSD patients compared with anti-AQP4 antibody-negative MS patients (70.4% vs. 26.5%) (Li et al., 2009). Among *H. pylori*-infected individuals, antibodies against *H. pylori* neutrophil-activating protein (NAP) were significantly more prevalent in anti-AQP4 antibody-positive NMOSD patients than in healthy subjects (36.8% vs. 2.8%) (see Fig. 2). Among anti-AQP4 antibody-positive NMOSD patients, a significant positive correlation between anti-*H. pylori*-NAP antibody levels and EDSS scores were found. In anti-*H. pylori*-NAP antibody-positive patients, EDSS scores were significantly higher than in anti-*H. pylori*-NAP antibody-negative patients (see Fig. 3). Interestingly, serum myeloperoxidase (MPO) levels were significantly higher in anti-*H. pylori*-NAP antibody-positive patients than in anti-*H. pylori*-NAP antibody-negative patients. These findings collectively suggest that *H. pylori* is an aggravating factor for NMOSD, and that *H. pylori*-NAP may be directly involved in exacerbating NMOSD. The positive association of *H. pylori* with NMOSD was also confirmed in a Chinese population—*H. pylori* seropositivity rates were significantly higher in anti-AQP4 antibody-positive NMOSD patients (93.1%) than in anti-AQP4 antibody-negative MS patients (80%) (Long et al., 2013). These findings suggest *H. pylori* infection is a risk factor for NMOSD, at least in East-Asian populations.

4. Mechanisms underlying the modulation of demyelinating disease by *Helicobacter pylori* infection

4.1. Multiple sclerosis

H. pylori is thought to be involved in the pathogenesis of MS in the context of the hygiene hypothesis but not as a direct involvement of the bacterium. The hygiene hypothesis was proposed to explain the increased prevalence of both autoimmune diseases and allergic diseases in industrialized countries during the last decades. The hygiene hypothesis suggests that low exposure to pathogens early in life might lead to a greater risk of immune-mediated diseases later in life (Strachan, 1989; Yazdanbakhsh et al., 2002).

H. pylori infection was reported to have an inverse correlation with the prevalence of atopic disorders (McCune et al., 2003), which is consistent with the hygiene hypothesis (Cremonini and Gasbarrini, 2003). Individuals infected with *H. pylori* were reported to be 30% less likely to have allergic diseases (McCune et al., 2003). A protective effect against allergy by *H. pylori* infection was assumed to be related to the generic exposure to pathogens, rather than with the specific infections. A bacterial infection can augment T helper 1 (Th1) and T helper 17 (Th17) responses while dampening T helper 2 (Th2) responses. Thus, infection reduces the frequency of allergic disorders. However, the incidences of Th1/Th17-type autoimmune diseases, such as RA (Kero et al., 2001), Crohn's disease (Kero et al., 2001) and type I diabetes mellitus (Stene and Nafstad, 2001), are high in patients with allergies. The frequencies of allergic disorders and autoimmune diseases are increasing in parallel in developed countries where good sanitation reduces the frequency of childhood infection. Less frequent bacterial infection is assumed to curtail the development of the immunoregulatory system in children, leading to an insufficient suppression of overactive allergen-specific Th2 cells as well as auto-reactive Th1/Th17 cells later in life (Yazdanbakhsh et al., 2002). The observation that people with an increased number of younger siblings during childhood have an increased risk of MS in Western populations (Ponsonby et al., 2005) suggests that encountering infection early in life renders individuals resistant to MS. Consequently, a lower frequency *of H. pylori* infection may be a reflection of good sanitation and a lower frequency of generic infection in MS patients.

However, several large cohort studies of childhood infection and MS risk argue against a lower incidence of childhood generic infection in MS. A Canadian longitudinal study found no relationship between birth order and MS risk (Sadovnick et al., 2005). A Danish MS registry study revealed that MS risk was not influenced by common childhood infection, such as measles, rubella, mumps, and varicella (Bager et al., 2004).

Intriguingly, Cook et al. found *H. pylori* infection in C58BL/6 mice reduced the severity of experimental autoimmune encephalomyelitis (EAE), an animal model of MS (Cook et al., 2015). In this model, interferon-gamma-producing Th1 cells and IL-17-producing Th17 cells were markedly decreased in the CNS and spleen by *H. pylori* infection. This report suggests that *H. pylori* directly exerts protective effects on acute neuroinflammation mediated by autoreactive Th1/Th17 cells. Recently, Efthymiou et al. examined immune responses against individual *H. pylori* antigens (Efthymiou et al., 2017). They found antibodies against 5 of 14 antigens, including p41, p54-flagellin, p29-UreA, p67-FSH, and p120-CagA, were less frequent in RRMS than in healthy controls, whereas anti-VacA antibodies were more frequent in SPMS than in healthy controls and anti-p54, p29-UreA, and anti-p26 antibody levels correlated with EDSS scores. This suggested that antibody

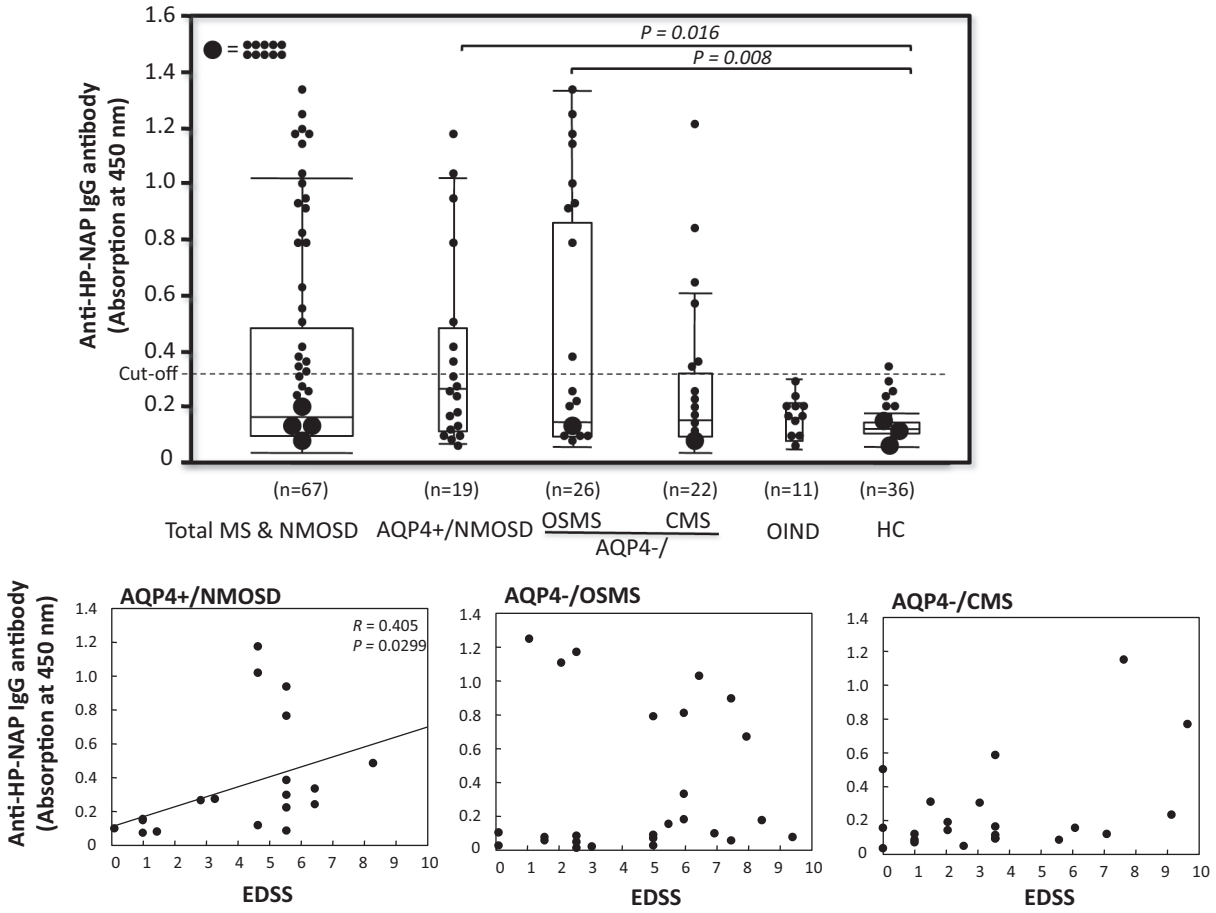

Fig. 2. Anti-*H. pylori*-NAP antibody levels in *H. pylori*-infected individuals and relationship between anti-*H. pylori*-NAP antibody levels and EDSS score in NMOSD and MS patients.

(A) Among anti-*H. pylori* antibody-positive subjects, anti-*H. pylori*-NAP antibody levels and positive frequencies are significantly higher in anti-AQP4 antibody-positive (AQP4 +) NMOSD patients and anti-AQP4 antibody-negative (AQP4-) OSMS patients than in healthy controls. The cut-off value is set at the mean absorbance of the HC group + 4SD. (B) Relationship between anti-*H. pylori*-NAP antibody levels and EDSS scores. In all MS patients and anti-AQP4 antibody-positive NMOSD patients, statistically significant positive correlations are seen between anti-*H. pylori*-NAP antibody levels and EDSS scores (Li et al., 2009). Ab, antibody; AQP4, aquaporin-4; CMS, conventional form of multiple sclerosis; HC, healthy controls; *H. pylori*, *Helicobacter pylori*; NAP, neutrophil-activating protein; OIND, other inflammatory neurological diseases; OSMS, opticospinal form of multiple sclerosis; SD, standard deviation.

responses may vary by *H. pylori* antigens and by MS subtypes—less frequent antibody positivity rates in RRMS are in accord with the above-mentioned protective effects of *H. pylori* while *H. pylori* antigens may be directly involved in disability progression of SPMS. Therefore, besides the MS protective effects of generic infection in childhood according to the hygiene hypothesis, *H. pylori* itself may be directly involved in the pathogenesis of MS according to subtype. Such a possibility is a matter of future studies.

4.2. Neuromyelitis optica spectrum disorders

H. pylori infection is increased in some chronic inflammatory diseases, such as ITP (Gasbarrini et al., 1998; Emilia et al., 2001), rheumatoid arthritis (Zentilin et al., 1999), and thyroiditis (de Luis et al., 1998). However, the mechanism involved in how *H. pylori* modulates these diseases remains to be elucidated. Current thought suggests that either a chronic inflammatory stimulus induced by *H. pylori* or cross mimicry between bacterial and host antigens are involved.

NMOSD is characterized by neutrophilic pleocytosis in the cerebrospinal fluid (CSF) (Ishizu et al., 2005). Spinal cord lesions of NMOSD are heavily infiltrated with myeloperoxidase-positive granulocytes (Lucchinetti et al., 2002; Ishizu et al., 2005). The IL-17/IL-8 system, which induces neutrophil activation and migration, is markedly upregulated in NMOSD CSF, irrespective of the presence or absence of anti-AQP4 antibody (Ishizu et al., 2005; Tanaka et al., 2008; Matsushita et al., 2013). We also reported that serum myeloperoxidase levels were significantly increased in NMOSD patients and were positively correlated with EDSS scores (Minohara et al., 2006). Furthermore, anti-AQP4 antibody-positive NMOSD patients have a high frequency of elevated C-reactive protein and hypercomplementemia in the relapse phase, which was also observed for the remission phase in about a third of NMOSD patients, indicating the persistent systemic inflammation of NMOSD patients (Doi et al., 2009). Thus, activated neutrophils and systemic inflammatory reactions might constitute an important part of the potent effector arm in NMOSD patients.

H. pylori strongly activates Th17 cells via the induction of IL-23 (Algood et al., 2007; Caruso et al., 2007), resulting in neutrophil mobilization and activation. *H. pylori*-NAP is a major proinflammatory protein responsible for the pathology of *H. pylori*-related gastric inflammatory diseases (Montecucco and de Bernard, 2003). High titers of antibody against *H. pylori*-NAP in NMOSD patients, regardless of the presence or absence of anti-AQP4 antibody (Li et al., 2009), suggests *H. pylori*-NAP is absorbed and presented to the host immune system. *H. pylori*-NAP that crossed epithelial monolayers induced the migration and activation of neutrophils (Montecucco and de Bernard, 2003). *H. pylori*-NAP acts directly on neutrophils and monocytes by promoting

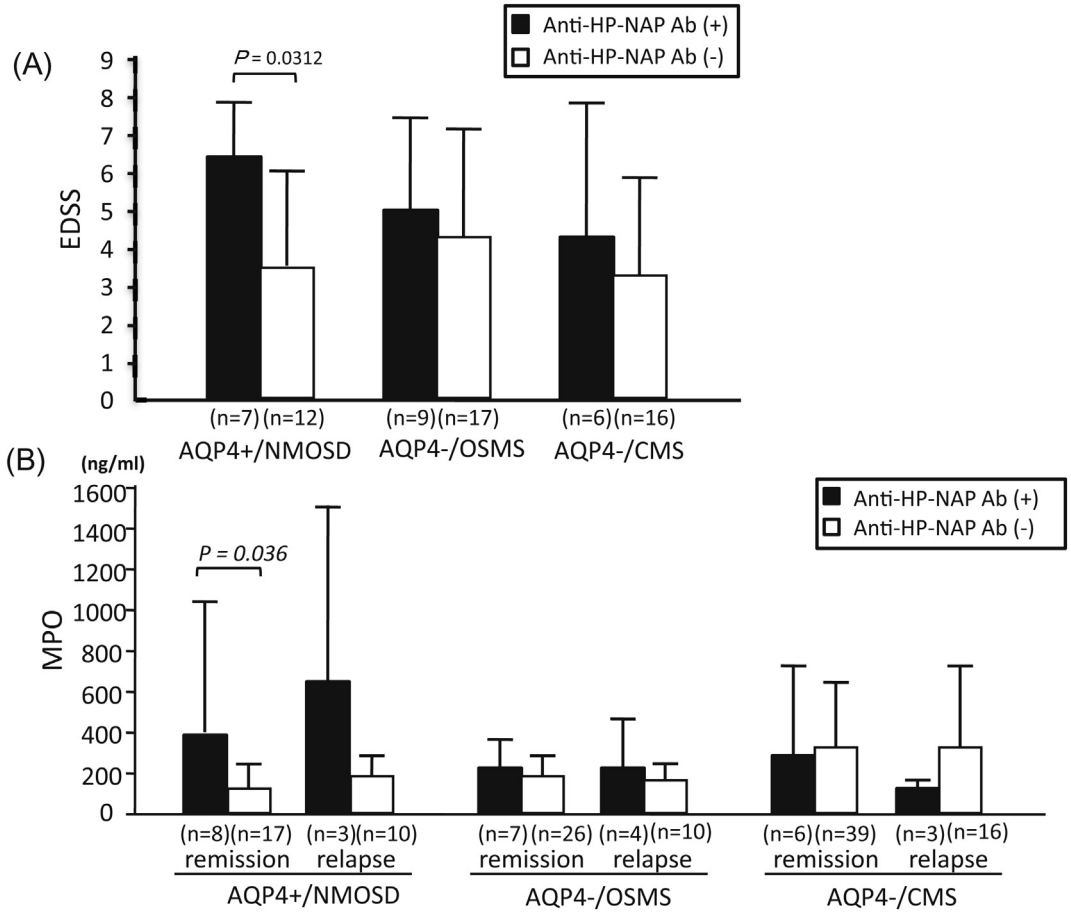

Fig. 3. EDSS scores and MPO levels according to anti-*H. pylori*-NAP antibody status.
(A) EDSS scores according to anti-*H. pylori*-NAP antibody status. Among the anti-AQP4 antibody-positive (AQP4+) NMOSD patient group, anti-*H. pylori*-NAP antibody-positive patients show significantly higher EDSS scores than anti-*H. pylori*-NAP antibody-negative patients. (B) Relationship between MPO levels and anti-*H. pylori*-NAP antibody seropositivity. In the anti-AQP4 antibody-positive NMOSD patient group, MPO levels are significantly higher in anti-*H. pylori*-NAP antibody-positive patients than in anti-*H. pylori*-NAP antibody-negative patients in the remission phase. A similar trend is also seen in the relapse phase (Li et al., 2009). Ab, antibody; AQP4, aquaporin-4; CMS, conventional form of multiple sclerosis; EDSS, Expanded Disability Status Scale of Kurtzke; HP, *Helicobacter pylori*; MPO, myeloperoxidase; NAP, neutrophil-activating protein; OSMS, opticospinal form of multiple sclerosis.

their recruitment and activation (Teneberg et al., 1997; Zanotti et al., 2002). In addition, it also induces mast cells to release proinflammatory mediators that activate neutrophils and monocytes (Teneberg et al., 1997; Zanotti et al., 2002). Given that anti-*H. pylori*-NAP antibody levels were positively correlated with final EDSS scores and myeloperoxidase levels in anti-AQP4 antibody-positive NMOSD patients (Li et al., 2009), *H. pylori*-NAP absorbed and presented to the host immune system may facilitate NMOSD development and exacerbation through the activation of neutrophils.

Because *H. pylori*-NAP itself is not bound by anti-AQP4 antibody, molecular mimicry between *H. pylori*-NAP and AQP4 is unlikely. However, bacteria harbor their own water channel proteins with some sequence homology to human AQP4 (Calamita, 2000). Molecular mimicry between human AQP4 and bacterial water channel proteins might be a possible source of cross-reactive antigens for anti-AQP4 antibody.

5. Conclusions

Many studies conducted in various Eastern and Western MS patients together with meta-analyses have indicated that *H. pylori* is a protective factor for MS. The protective effects of *H. pylori* were more evident in low prevalence countries and in younger generations that grew up in the low prevalence era. This is in accord with the hygiene hypothesis, indicating that a generic infection in early childhood renders subjects resistant to MS through sufficient maturation of the immunoregulatory system. However, no effects of common childhood infections on MS risk reported by large MS cohort studies, and the direct attenuation of autoreactive Th1 and Th17 cells by *H. pylori* infection in EAE may underscore the direct protective effects *H. pylori* itself rather than generic infection in childhood. By contrast, *H. pylori* infection and its proinflammatory proteins, such as NAP, may contribute to the pathology of anti-AQP4 antibody-related neural damage, by acting as a systemic inflammatory stimulus targeting neutrophils. Similar exacerbating effects of *H. pylori* on disability progression in SPMS warrants further large-scale studies.

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References

Algood, H.M., Gallo-Romero, J., Wilson, K.T., Peek Jr., R.M., Cover, T.L., 2007. Host response to helicobacter pylori infection before initiation of the adaptive immune response. FEMS Immunol. Med. Microbiol. 51, 577–586.

Apostolopoulos, P.1., Vafiadis-Zouboulis, I., Tzivras, M., Kourtessas, D., Katsilambros, N., Archimandritis, A., 2002. Helicobacter pylori (H. Pylori) infection in Greexe: the changing prevalence during a ten-year period and its antigenic profile. BMC Gastroenterol. 2, 11.

Asaka, M., Kimura, T., Kudo, M., Takeda, H., Mitani, S., Miyazaki, T., et al., 1992. Relationship of helicobacter pylori to serum pepsinogens in an asymptomatic Japanese population. Gastroenterology 102, 760–766.

Atherton, J.C., 2006. The pathogenesis of helicobacter pylori-induced gastroduodenal diseases. Annu. Rev. Pathol. 1, 63–96.

Bager, P., Nielsen, N.M., Bihrmann, K., 2004. Childhood infections and risk of multiple sclerosis. Brain 127, 2491–2497.

Blaser, M.J., 1993. Helicobacter pylori: microbiology of a 'slow' bacterial infection. Trends Microbiol. 1, 255–260.

Calamita, G., 2000. The Escherichia coli aquaporin-Z water channel. Mol. Microbiol. 37, 254–262.

Caruso, R., Pallone, F., Monteleone, G., 2007. Emerging role of IL-23/IL-17 axis in H pylori-associated pathology. World J. Gastroenterol. 13, 5547–5551.

Cook, K.W., Crooks, J., O'Brien, K., Braitch, M., Kareem, H., Constantinescu, C.S., et al., 2015. Helicobacter pylori infection reduces disease severity in an experimental model of multiple sclerosis. Front. Microbiol. http://dx.doi.org/10.3389/fmicb.2015.00052.

Cremonini, F., Gasbarrini, A., 2003. Atopy, *Helicobacter pylori* and the hygiene hypothesis. Eur. J. Gastroenterol. Hepatol. 15, 635–636.

de Luis, D.A., Varela, C., de La Calle, H., Cantón, R., de Argila, C.M., San Roman, A.L., et al., 1998. Helicobacter pylori infection is markedly increased in patients with autoimmune atrophic thyroiditis. J. Clin. Gastroenterol. 26, 259–263.

Doi, H., Matsushita, T., Isobe, N., Matsuoka, T., Minohara, M., Ochi, H., et al., 2009. Hypercomplementemia at relapse in patients with anti-aquaporin-4 antibody. Mult. Scler. 15, 304–310.

Ebers, G.C., 2008. Environmental factors and multiple sclerosis. Lancet Neurol. 7, 268–277.

Efthymiou, G., Dardiotis, E., Liaskos, C., Marou, E., Tsimourtou, V., Rigopoulou, E.I., et al., 2017. Immune responses against helicobacter pylori-specific antigens differentiate relapsing remitting from secondary progressive multiple sclerosis. Sci. Rep. 7 (7929). http://dx.doi.org/10.1038/s41598-017-07801-9.

Emilia, G., Longo, G., Luppi, M., Gandini, G., Morselli, M., Ferrara, L., et al., 2001. Helicobacter pylori eradication can induce platelet recovery in idiopathic thrombocytopenic purpura. Blood 97, 812–814.

Ford, A.C., Forman, D., Hunt, R., Yuan, Y., Moayyedi, P., 2015. Helicobacter pylori eradication for the prevention of gastric neoplasia. Cochrane Database Syst. Rev. 7, CD005583.

Fujimura, K., Kuwana, M., Kurata, Y., Imamura, M., Harada, H., Sakamaki, H., et al., 2005. Is eradication therapy useful as the first line of treatment in helicobacter pylori idiopathic thrombocytopenic purpura? Analysis of 207 eradicated chronic ITL cases in Japan. Int. J. Hematol. 81, 162–168.

Gasbarrini, A., Franceschi, F., Tartaglione, R., Landolfi, R., Pola, P., Gasbarrini, G., 1998. Regression of autoimmune thrombocytopenia after eradication of helicobacter pylori. Lancet 352 (9131), 878.

Gavalas, E., Kountouras, J., Deretzi, G., Boziki, M., Grigoriadis, N., Zavos, C., et al., 2007. *Helicobacter pylori* and multiple sclerosis. J. Neuroimmunol. 188, 187–189.

Graham, D.Y., 1991. Helicobacter pylori: its epidemiology and its role in duodenal ulcer disease. J. Gastroentrol. Hepatol. 6, 105–113.

Hasni, S.A., 2012. Role of helicobacter pylori infection in autoimmune diseases. Curr. Opin. Rheumatol. 24, 429–434.

Ishizu, T., Osoegawa, M., Mei, F.J., Kikuchi, H., Tanaka, M., Takakura, Y., et al., 2005. Intrathecal activation of the IL-17/IL-8 axis in opticospinal multiple sclerosis. Brain 128, 988–1002.

Jaruvongvanich, V., Sanguankeo, A., Jaruvongvanich, S., Upala, S., 2016. Assocation between helicobacter pylori infection and multiple sclerosis: a systematic review and meta-analysis. Mult. Scler. Relat. Disord. 7, 92–97.

Kero, J., Gissler, M., Hemminki, E., Isolauri, E., 2001. Could TH1 and TH2 diseases coexist? Evaluation of asthma incidence in children with celiac disease, type 1 diabetes, or rheumatoid arthritis: a register study. J. Allergy Clin. Immunol. 108, 781–783.

Kiefel, V., Santoso, S., Kaufmann, E., Mueller-Eckhardt, C., 1991. Autoantibodies against platelet glycoprotein I1/IX: a frequent finding in autoimmune thrombocytopenic purpura. Br. J. Haematol. 79, 256–262.

Kira, J., 2012. Genetic and environmental backgrounds responsible for the change in the phenotype of MS in Japanese subjects. Mult. Scler. Relat. Disord. 1, 188–195.

Kira, J., 2013. Genetic and environmental factors underlying the rapid changes in epidemiological and clinical features of multiple sclerosis and neuromyelitis optica in Japanese. Clin. Exp. Neuroimmunol. 4, 261–273.

Lee, Y.C., Chiang, T.H., Chou, C.K. Lee Y.C., Chiang, T.H., Chou, C.K., et al., 2016. Association between helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology 150, 1113–1124 (e1115).

Lennon, V.A., Wingerchuk, D.M., Kryzer, T.J., Pittock, S.J., Lucchinetti, C.F., Fujihara, K., et al., 2004. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 364, 2106–2112.

Lennon, V.A., Kryzer, T.J., Pittock, S.J., Verkman, A.S., Hinson, S.R., 2005. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J. Exp. Med. 202, 473–477.

Li, W., Minohara, M., Su, J.J., Matsuoka, T., Osoegawa, M., Ishizu, T., et al., 2007. Helicobacter pylori infection is a potential protective factor against conventional multiple sclerosis in the Japanese population. J. Neuroimmunol. 184, 227–231.

Li, W., Minohara, M., Piao, H., Matsushita, T., Masaki, K., Matsuoka, T., et al., 2009. Association of anti-helicobacter pylori neutrophil-activating protein antibody response with anti-aquaporin-4 autoimmunity in Japanese patients with multiple sclerosis and neuromyelitis optica. Mult. Scler. 15 (14111-1421).

Long, Y., Gao, C., Qiu, W., Hu, X., Shu, Y., Peng, F., et al., 2013. Helicobacter pylori infection in neuromyelitis optica and multiple sclerosis. Neuroimmunomodulation 20, 107–112.

Lucchinetti, C.F., Mandler, R.N., McGavern, D., Brück, W., Gleich, G., Ransohoff, R.M., et al., 2002. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain 125, 1450–1461.

Malli, C., Pandit, L., D'Cunha, A., Mustafa, S., 2015. Environmental factors related to multiple sclerosis in Indian population. PLoS ONE 10 (4) e0124064. 10.137/journal.pone.0124064.

Matsushita, T., Tateishi, T., Isobe, N., Yonekawa, T., Yamasaki, R., Matsuse, D., et al., 2013. Characteristic cerebrospinal fluid cytokine/chemokine profiles in neuromyelitis optica, relapsing remitting or primary progressive multiple sclerosis. PLoS ONE 8 (4), e61835.

McCune, A., Lane, A., Murray, L., Harvey, I., Nair, P., Donovan, J., et al., 2003. Reduced risk of atopic disorders in adults with helicobacter pylori infection. Eur. J. Gastroenterol. Hepatol. 15, 637–640.

McMillan, R., Tani, P., Millard, F., Berchtold, P., Renshaw, L., Woods, V.L.Jr, 1987. Platelet-associated and plasma antiglycoprotein autoantibodies in chronic ITP. Blood 70, 1040–1045.

Minohara, M., Matsuoka, T., Li, W., Osoegawa, M., Ishizu, T., Ohyagi, Y., Eta, al., 2006. Upregulation of myeloperoxidase in patients with opticospinal multiple sclerosis: positive correlation with disease severity. J. Neuroimmunol. 178, 156–160.

Mohebi, N., Mamarabadi, M., Mohgaddasi, M., 2013. Relation of helicobacter pylori and multiple sclerosis in Iranian patients. Neurol. Int. 5, e10.

Montecucco, C., de Bernard, M., 2003. Molecular and cellular mechanisms of action of the vacuolating cytotoxin (Vac a) and neutrophil-activating protein (HP-NAP) virulence factors of helicobacter pylori. Microbes Infect. 5, 715–721.

Osoegawa, M., Kira, J., Fukazawa, T., Fujihara, K., Kikuchi, S., Matsui, M., et al., 2009. Temporal changes and geographical differences in multiple sclerosis phenotypes in Japanese: nationwide survey results over 30 years. Mult. Scler. 15, 159–173.

Pedrini, M.J.F., Seewann, A., Bennett, K.A., Wood, A.J.T., James, I., Burton, J., et al., 2015. Helicobacter pylori infection as a protective factor against multiple sclerosis risk in females. J. Neurol. Neurosurg. Psychiatry 86, 603–607.

Pereira, M.-I., Medeiros, J.A., 2014. Role of helicobacter pylori in gastric mucosa-associated lymphoid tissue lymphomas. World J. Gastroenterol. 20, 684–698.

Ponsonby, A.L., van der Mei, I., Dwyer, T., Blizzard, L., Taylor, B., Kemp, A., et al., 2005. Exposure to infant siblings during early life and risk of multiple sclerosis. JAMA 26, 463–469.

Sadovnick, A.D., Yee, I.M., Ebers, G.C., 2005. Multiple sclerosis and birth order: a longitudinal cohort study. Lancet Neurol. 4, 611–617.

Salama, N.R., Hartung, M.L., Müller, A., 2013. Life in the human stomach: persistence strategies of the bacterial pathogen helicobacter pylori. Nat. Rev. Microbiol. 11, 385–399.

Salim, M.A., Eftekharian, M.M., Taheri, M., Alikhani, M.Y., 2017. Determining the IgM and IgG antibody titer against CMV and helicobacter pylori in the serum of multiple sclerosis patients comparing to the control group in Hamadan. Hum. Antibodies 26, 23–28.

Stene, L.C., Nafstad, P., 2001. Relation between occurrence of type 1 diabetes and asthma. Lancet 357, 607–608.

Strachan, D.P., 1989. Hay fever, hygiene, and household size. Br. Med. J. 299, 1259–1260.

Tanaka, M., Matsushita, T., Tateishi, T., Ochi, H., Kawano, Y., Mei, F.J., et al., 2008. Distinct CSF cytokine/chemokine profiles in atopic myelitis and other causes of myelitis. Neurology 71, 974–981.

Teneberg, S., Miller-Podraza, H., Lampert, H.C., Evans Jr., D.J., Evans, D.G., Danielsson, D., et al., 1997. Carbohydrate binding specificity of the neutrophil-activating protein of helicobacter pylori. J. Biol. Chem. 272, 19067–19071.

Tomiyama, Y., Kosugi, S., 2005. Autoantigenic epitopes on platelet glycoproteins. Int. J. Haematol. 81, 100–105.

Wingerchuk, D.M., Banwell, B., Bennett, J.L., Cabre, P., Carroll, W., Chitnis, T., et al., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85, 177–189.

Yao, G., Wang, P., Luo, X.-D., Yu, T.-M., Harris, R.A., Zhang, X.-M., 2016. Meta-analysis of association between helicobacter pylori infection and multiple sclerosis. Neurosci. Lett. 620, 1–7.

Yazdanbakhsh, M., Kremsner, P.G., van Ree, R., 2002. Allergy, parasites, and the hygiene hypothesis. Science 296, 490–494.

Yoshimura, S., Isobe, N., Yonekawa, T., Matsushita, T., Masaki, K., Sato, S., et al., 2012. Genetic and infectious profiles of Japanese multiple sclerosis patients. PLoS ONE 7, e48592.

Yoshimura, S., Yonekawa, T., Isobe, N., Matsushita, T., Kira, J., 2013. Bacterial infectious burden and prevalence of idiopathic central nervous system demyelinating diseases in Japanese. Clin. Exp. Neuroimmunol. 4, 351–352.

Yoshimura, S., Isobe, N., Matsushita, T., Masaki, K., Sato, S., Kawano, Y., et al., 2014. Genetic and infeactious profiles influence cerebrospinal fluid IgG abnormality in Japanese multiple sclerosis patients. PLoS ONE 9, e95367.

Zanotti, G.1., Papinutto, E., Dundon, W., Battistutta, R., Seveso, M., Giudice, G., et al., 2002. Structure of the neutrophil-activating protein from helicobacter pylori. J. Mol. Biol. 323, 125–130.

Zentilin, P., Savarino, V., Garnero, A., Accardo, S., Seriolo, B., 1999. Is helicobacter pylori infection a risk factor for disease severity in rheumatoid arthritis? Gastroenterology 116, 503–504.