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Environmental factors influencing multiple sclerosis in Latin America

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Abstract

It is generally accepted that autoimmune diseases like multiple sclerosis (MS) arise from complex interactions between genetic susceptibility and environmental factors. Genetic variants confer predisposition to develop MS, but cannot be therapeutically modified. On the other hand, several studies have shown that different lifestyle and environmental factors influence disease development, as well as activity levels and progression. Unlike genetic risk factors, these can be modified, with potential for prevention, particularly in high-risk populations. Most studies identifying particular lifestyle and environmental factors have been carried out in Caucasian patients with MS. Little or no data is available on the behavior of these factors in Latin American populations. Ethnic and geographic differences between Latin America and other world regions suggest potential regional variations in MS, at least with respect to some of these factors. Furthermore, particular environmental characteristics observed more frequently in Latin America could explain regional differences in MS prevalence. Site-specific studies exploring influences of local environmental factors are warranted.

Keywords: Environmental factors, Epstein–Barr virus, helminth infections, hygiene hypothesis, multiple sclerosis, smoking, Vitamin D

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Introduction

Pathogenic mechanisms underlying multiple sclerosis (MS) development have yet to be clearly identified, but considerable evidence indicates autoimmunity plays an important role in MS etiology.[1] It is generally accepted that autoimmune diseases like MS arise from complex interactions between individual genetic susceptibility and environmental factors. In Caucasian populations, the strongest genetic link to MS has been found in MHC haplotypes, especially those containing *HLA-DRB1*15.01*, *HLA DQB1*06.02*, and *DQA1*01.02*. Genome-wide association studies have identified more than 100 non-HLA genetic risk loci, many acting as cooperative networks. However, each of these individual loci exerts modest influence on MS risk, and MHC remains the key susceptibility locus.[2] Furthermore, in studies of identical twins where one develops MS, only 30% of second twins developed the disease.[3] Discordance between monozygotic twins suggests additional factors such as environmental modulators could be involved.

The strongest evidence favoring environmental influence on MS development is the unusual geographic distribution of the disease. Prevalence rates are increased in high-latitude regions, and uncommon near the equator, giving rise to a north–south prevalence gradient in the northern hemisphere. However, gradient magnitude has declined in recent years in the United States and western Europe.[4] Likewise, MS prevalence in the north of Mexico (low to medium) contrasts with that in the southeast of Texas, USA (high), even though both zones are located at the same latitude.[5,6]

Little information is available on Latin America, although genomic variations among local populations might explain a southern hemisphere gradient for MS. Genetic characteristics of MS in Latin America are unique because of the intermarriage between Amerindians, Caucasians and Africans which has led to marked racial heterogeneity. More southern regions (Argentina and Uruguay) have more Caucasian haplotypes, commonly associated

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with MS. However, in the rest of Latin America ancestral genetic components differ significantly. Mestizos, for example, represent a complex admixture of Caucasian and Amerindian (mongoloid) genes.[7] MS is uncommon among pure Amerindians in the region.[8,9] Perhaps Amerindians are protected against MS by their mongoloid genes, as has been observed in Canadian aboriginals and Japanese cohorts.[10,11] African immigrants to America marrying Caucasians is the source of yet another distinct racial group in Latin America: the mulattos. This population is prominent in the Caribbean islands, Central American countries and parts of South America. Higher rates of MS among mestizos and mulattos probably results from increased Caucasian genetic influence; Mexican mestizos, for example, share *HLA-DRB1* gene levels that are similar to Caucasian populations at high risk.[12] Likewise, an association has also been found between MS and the *DQA1*01:02* and *DQB1*06:02* haplotypes in African-Brazilian patients where the *DRB1*15:01* allele was absent.[13] Most of these patients have European ancestors, suggesting these alleles were acquired by intermarriage with Caucasian populations. In contrast, the frequency of these haplotypes in native populations is very low, indicating genetic admixture between Amerindians or African Brazilians and Caucasians probably occurred in last five centuries.[14,15]

In the southern hemisphere, while the latitude gradient has remained strong in Australia,[16] no south–north gradient has been observed in the Argentine Patagonia between parallels 55° and 36°S.[17] In view of the substantial immigration to Australia in recent years, the question arises as to whether some of the prevalence gradient may have resulted from an uneven distribution of immigrants, most of whom came from the UK and Ireland.[18] In contrast, in the Argentine Patagonia the absence of a south–north gradient could be attributed to rapid demographic growth of the region resulting from native population migrants from neighboring countries and other Argentine provinces, making it difficult to determine whether exposure to potential environmental risk factors lasted long enough to modify disease incidence. The fact that there is significant correlation between latitude and prevalence for regions of European descent, but not for regions of largely non-European descent, suggests the presence of gene–environment interactions.[19] This is not altogether unexpected, given the higher frequencies of high-risk alleles for MS in European populations.

In addition, population migration studies indicate individuals moving from low to high-risk areas, particularly before the age of 15, show similar incidence to host country populations, suggesting the presence of either a protective factor in the region of origin, or alternatively, a harmful factor in the adopted region.[20]

Serial cross-sectional studies comparing MS epidemiology from various continents provide compelling evidence for a significant rise both in MS incidence and prevalence in recent decades.[21] Given the short period of time over which these population changes have occurred, genetic factors seem an unlikely cause, whereas epidemiological studies appear to indicate MS risk is influenced by the environment. Unlike genetic risk factors, many environmental and lifestyle factors can be modified. Information on protective and disease-triggering factors should be incorporated into patient care and perhaps even into prevention campaigns, particularly for individuals referring family history of MS and therefore increased risk of developing the disease.

The low to medium prevalence rates found in Latin America, compared with North American and European countries, suggest ethnicity (in particular, indigenous ancestry) or differences in environmental factors (or both) could influence the distribution of MS prevalence in the region. In addition, significant variability both in socioeconomic conditions and access to health care should be considered as additional potential factors explaining these differences. The main environmental risk factors investigated in different countries of Latin America are summarized in Table 1.

Ultraviolet radiation and Vitamin D levels

The observation that MS is more common as distance from the equator increases led to a link being drawn to variation in levels of ultraviolet radiation (UVR).[22] Several studies largely confirmed the association between lower sun exposure and MS risk, and animal studies suggested the protective effect was mediated by vitamin D. However, the vitamin D precursor is not the only chromophore in the skin; other UVR-induced products have biological effects likely to be relevant in MS.[23] 7-dehydrocholesterol is converted to pre-vitamin D, and trans-urocanic acid (UCA) is converted to cis-UCA.[24,25] Both molecules have important immunomodulatory effects. It has now been well established that the physiological relevance of vitamin D extends beyond calcium homeostasis regulation, and plays an important role in the modulation of the immune system.[24] A protective effect of vitamin D on MS is supported by the reduced risk associated with sunlight exposure and use of vitamin D supplements.[26,27] Moreover, high circulating levels

Table 1. Environmental and lifestyle risk factors for MS studied in Latin America.

Factor	Country	Main findings	Reference
Vitamin D /Sunlight exposure	Argentina	Levels of $25(OH)D_3$ and$1,25(OH)_2D_3$, measured by ELISA were significantly lower in relapsing–remitting patients than in controls. In addition, levels in patients suffering relapse were lower than during remissions. In contrast, primary progressive patients showed similar values to controls.	24
	Mexico	In a tropical country, no association between sunlight exposure and risk of developing MS was observed, even after considering immunological effects caused by UV radiation and/or changes in vitamin D metabolism.	40
	Brazil	Vitamin D serum levels in MS patients were similar to the summer, but lower in winter than those of healthy individuals.	37
	Ecuador	No statistically significant differences in vitamin D serum levels were observed between patients with MS and individuals from the general population	99
	Argentina	cis-UCA appears to be an additional UV-mediated immunomodulator. Plasma levels of cis-UCA were significantly lower in MS patients compared with controls.	25
Melatonin	Argentina	Melatonin levels, modulated by seasonal variations in night duration, negatively correlated with multiple sclerosis activity in humans. Melatonin ameliorated multiple sclerosis by controlling the balance between regulatory and effector cells, suggesting melatonin-triggered signaling pathways are potential targets for therapeutic intervention.	36
Helminths	Argentina	During a 4.6-year follow-up period, parasite-infected MS patients showed significantly lower number of exacerbations, minimal variation in disability scores, as well as fewer MRI changes when compared with uninfected MS patients.	51
	Argentina	Helminth-infection control was associated with significant increase in clinical and radiological MS activity. These observations suggest parasite regulation of host immunity can alter the course of MS.	48
	French West Indies	Increased MS incidence in the region, in association with significant reduction of parasite infections.	46
Viral infections	Argentina	Significant association between systemic viral and bacterial infections, and risk of MS relapse, increased MRI activity, and T-cell activation.	95
	Mexico	Epidemiological studies from geographical areas where incidence of MS has increased in recent decades indicated high frequency of varicella and zoster (VZV) infections in personal history of MS patients. Serum biochemistry showed large quantities of DNA from VZV in leucocytes and cerebrospinal fluid of MS patients restricted to the ephemeral period of MS relapse, followed by disappearance of the virus during remission.	66, 67
EBV infections	Mexico	No differences were observed between MS and healthy controls in terms of the presence of EBV DNA in peripheral blood mononuclear cells.	63

(continued)

Table 1. Continued

Factor	Country	Main findings	Reference
	Brazil	98.5% of Brazilian patients with MS were IgG positive for EBV, but none was IgM positive for EBV. These results are similar to those found in other countries.	100
Smoking	Argentina	Cigarette smoking was a risk factor for early conversion to clinically definite MS among patients with CIS, and disease progression was more rapid in ever-smoker patients compared with non-smokers. Moreover, MS patients who smoked had significantly higher risk of attaining EDSS score 4 and 6, compared with non-smoker MS patients.	93
Salt intake	Argentina	Positive correlation was observed between exacerbation and sodium intake. Exacerbation rates were 2.75-fold or 3.95-fold higher in patients with medium or high sodium intake compared with low intake. Individuals with high sodium intake had a 3.4-fold greater chance of developing a new lesion on MR imaging.	87
ART	Argentina	ART was associated with a 7-fold increase in risk of MS exacerbation, and a 9-fold increase in risk of enhanced disease activity on MRI.	101
Obesity	Argentina	As in other populations, obesity in adolescence/early adulthood is associated with increased risk of MS.	102
Fatty acids	Mexico	Omega-3 polyunsaturated fatty acid supplementation is highly effective in reducing cytokine and nitric oxide catabolite levels in patients with relapsing–remitting MS.	82

ART: Assisted reproductive technology.

of 25-hydroxy-vitamin D (25(OH)D), a measure of vitamin D status, have been associated with lower risk of MS,[28] in particular before the age of 20, and recent studies in patients with MS found that higher serum levels of 25(OH)D (>40 ng/ml or more than 100 nMol/l) correlated with fewer magnetic resonance imaging (MRI) lesions and relapses.[29] Furthermore, serum levels of 25(OH)D are lower during MS relapses than remissions, and correlate inversely with clinical and radiological disease severity.[30]

Genetic data also point to the influence of vitamin D on immune regulation. Vitamin D response elements have been identified in the promoter region of the *HLA-DRB1*1501* allele, suggesting vitamin D may play a role in regulating the genetic locus most implicated in MS risk.[31] Furthermore, polymorphisms in a central vitamin D metabolism enzyme gene *CYP27B1* are associated with increased risk of MS.[32]

Despite considerable evidence of lower 25(OH)D levels in people with more active MS, vitamin D supplementation trials have shown disappointing results.[33] Issues of sample size, inadequate vitamin D dosing and lack of randomization may explain the conflicting results. Larger clinical trials on vitamin D supplementation are currently underway.

Most epidemiological studies focusing on the impact of sun exposure and vitamin D levels in MS development were performed in Caucasian populations. Very little information is available on Latin America populations, which have great genotypic and phenotypic variability.

Seasonal differences in MS activity have been reported and are contradictory in relation to a protective role for vitamin D. Along with the predicted correlation between sun exposure and increased levels of vitamin D, which would suggest higher disease activity during low sun exposure seasons such as fall and winter,[34] other recent studies suggest the opposite, namely that disease activity increases during spring and summer.[35,36] A mechanistic explanation for this observation has been offered in a study correlating disease activity with melatonin. In MS, melatonin levels negatively correlate with disease activity, most likely by blocking of Th17 cells and induction of Tr1 differentiation.[36]

In a Brazilian study, seasonal variation of vitamin D levels was shown. During winter, patients with MS had lower levels of vitamin D than controls and increased disease activity, characterized by the onset of relapses or new Gadolinium-enhancing lesions.[37] Interestingly, mean concentration of vitamin D in summer (around 74 nmol/l) was very similar to levels detected in patients in New Zealand (74 nmol/l) and Germany (67 nmol/l) during the same season. However, vitamin D serum concentrations during the winter were higher (around 61 nmol/l) than concentrations observed in New Zealand (32 nmol/l) and Germany (42 nmol/l) in the same season.[38] Brazil gets more sunlight throughout the year than other areas with high incidence of MS. Higher and more stable levels of UVR/vitamin D than in other geographical areas may play a role in the lower incidence of MS in this country.

At our center in Buenos Aires (latitude 34°S, longitude 58°W), Argentina, we observed that in Hispanic individuals, higher levels of vitamin D were associated with remissions (range 115–120 nmol/l), whereas lower concentrations of vitamin D correlated with relapses (96–98 nmol/l).[24] Inverse correlation between vitamin D serum concentration and clinical disease severity has been previously reported. However, vitamin D concentration values detected in our population were different to results reported in other countries. In Finland, for example, lower concentrations of vitamin D were found during remissions (60 nmol/l) and much lower concentrations during relapses (44–47 nmol/l), with no relapses observed for values above 85 nmol/l.[39] Higher concentrations of vitamin D in our population may contribute to the lower incidence of MS found in Argentina in comparison with Finland. On the other hand, despite the fact that UVR exposure is greater in Brazil than in Argentina, mean vitamin D concentration levels were higher in our cohort than the one studied in Brazil. This finding is in contradiction with the greater incidence of MS reported in Argentina compared with Brazil. Similarly, no association between sunlight exposure and risk of MS was found in a Mexican cohort.[40] It would appear that latitude, UVR and levels of vitamin D do not exert the same effect on Latin American populations as those observed in Caucasian ones. For example, Cuba is at lower latitude in relation to Monterrey (Mexico) but has higher prevalence of MS (7.5 vs. 25 per 100,000, respectively).[41] Similarly, Punta Arenas, located at latitude 53°S, has a lower prevalence of MS than Montevideo and Buenos Aires, both located at latitude 34°S.[28] Therefore, it appears that in Latin America, latitude, UVR and vitamin D levels do not have the same immunomodulatory effects across the region, and consequently do not influence MS prevalence to the same degree as in other parts of the world.

The hygiene hypothesis and the influence of parasite infections on MS course

An ongoing debate persists as to whether infections prevent or precipitate autoimmune diseases. Microbial infections can act as environmental triggers inducing or promoting autoimmunity, resulting in clinical manifestations of autoimmune disease in genetically predisposed individuals. Alternatively, infectious diseases might accelerate established, but sub-clinical, autoimmune processes.[42]

Conversely, however, certain epidemiological and experimental studies support the hygiene hypothesis, which considers infections to protect rather than induce or accelerate autoimmune diseases like MS.[43] In line with this concept, Leibowitz and coworkers suggested in 1966 that greater MS prevalence correlated with higher sanitation levels in childhood environments.[44] Support for this hypothesis comes from epidemiological data demonstrating an inverse relation between infections and allergies, as well as autoimmune diseases, in the developed world between 1950 and 2000, even after adjusting for improvements in access to health care and diagnostic capabilities.[43] Additional epidemiological investigations demonstrate an inverse correlation between global distribution of MS and that of the parasite *Trichuris trichiura*, a common human pathogen. MS prevalence appears to fall steeply once a critical threshold of *T. trichiura* prevalence (about 10%) is exceeded in any given population.[45] Thus, dichotomous distribution of MS and *T. trichiura* infection would hint at helminth-induced protection against MS development. Indeed, regions of the world where poor sanitary conditions generate endemic areas of parasitoses show lower prevalence of allergic and autoimmune diseases. In line with the hygiene hypothesis, longitudinal and migratory studies evaluating MS prevalence, such as those conducted in the French West Indies between 1978 and 1994, showed increased MS incidence in the region in association with significant reduction of parasite infections during the same time period.[46] In addition, interventional studies report that individuals whose infections clear after anti-helminth drug administration show increased skin reactivity to different allergens as well as increased MS activity, indicating once again that helminths appear to directly suppress allergic reactions and autoimmune diseases.[47,48]

Overall, these observations suggest that elimination of regulatory effects resulting from microorganism and parasite infection in populations adapted to living with them tends to cause immune system imbalance and increase immune-mediated disease incidence. The protective effect of helminths might, at least in part, depend on parasite load. Elevated numbers of organisms may trigger regulatory circuits, while lower ones may act as immune adjuvants, enhancing allergic and autoimmune sensitization.

Consequently, the question arises as to whether helminths should be considered harmful pathogens or beneficial commensals.[49] A limitation of the hygiene hypothesis in MS arises from the Epstein–Barr virus (EBV) paradox, namely the extremely low risk for MS among individuals who are EBV seronegative. According to the hygiene hypothesis, these individuals should have high MS risk; paradoxically, their MS risk is much lower than that of their EBV-positive peers.[50]

In Buenos Aires, Argentina, we demonstrated that parasite-infected MS patients showed significantly lower number of relapses, minimal changes in disability scores and significantly lower MRI activity compared with uninfected MS individuals.[51] Parasite infections are often long-lived and inhabit immunocompetent hosts; consequently, it is not surprising that parasites may have developed modulatory molecules ameliorating host responses, thus enhancing their survival. In our study, parasite-driven protection was associated with induction of regulatory T cells and B cells secreting suppressive cytokines such as IL-10 and TGF-β, as well as $CD4^+$ $CD25^+$ $FoxP3^+$ regulatory T cells displaying significant suppressive function.[52] These observations allow us to hypothesize that in low-resource settings, such as those in many areas of Latin America, the presence of helminth infections could be a contributing factor to explain, at least in part, the lower regional prevalence of MS.

The protective effects of parasitic infections and the deleterious effect of deworming on the MS course have not been studied extensively, partly because helminth infection prevalence and MS show little overlap. At this stage, both beneficial and deleterious consequences of helminth infection need to be more clearly identified. Individual species may develop very different infection dynamics over time, and/or during peak infection intensity. Moreover, the same species may trigger opposite effects under varying conditions. For example, if susceptibility to autoimmune diseases is genetically influenced, propensity to infection may also modulate immune response, making particular infections protective only in certain genotypes, rather than in the population at large. It is evident that future studies in this area will be required to establish whether certain infections, particularly those produced by helminths during critical periods of infancy, truly exert a protective effect against MS. Finally, these observations raise a paradox, namely that deworming populations with helminth-associated morbidity could cause emergence of chronic inflammatory conditions and autoimmune diseases.[49,53]

Epstein–Barr virus infection

EBV is double-strand DNA virus of the herpes family infecting 90% of the general population in first decade of life, persisting latently and permanently in B-cell memory. Primary infection usually occurs at early age through saliva without any symptoms. However, in up to 40% of adolescents and adults, primary infection leads to infectious mononucleosis (IM).[54]

MS epidemiology suggests a relationship between EBV and MS, due to the similarities between IM and MS in terms of geographical distribution, age, race, and socioeconomic status.[55] Nevertheless, several other infectious agents have been proposed to explain the epidemiological features of MS. Although the particular contribution of other infections is unclear, in the case of EBV, the hypothesis suggests that contracting the infection later in life, with or without IM, might increase risk of MS. Several reports support this claim. First, individuals with known history of IM, have a 2–3 times higher risk of developing MS.[56] Second, individuals not infected by EBV or negative for EBV serology have an extremely low risk of developing MS.[57] Third, a report following US recruits showed that MS risk is extremely low among EBV-seronegative individuals, and that during follow-up, those who developed MS had become seropositive in the months prior to first MS symptoms.[58] Finally, extensive serological analysis has led to the conclusion that EBV-negative MS patients (if they exist at all), represent less than 0.01% of all individuals with MS.[59] Therefore, although EBV infection does not explain the totality of MS risk, it seems to constitute a necessary event to develop the disease.[60]

Mechanistic evidence supporting epidemiological association between MS and EBV infection is ill-defined. Several hypotheses have been proposed, however, including: over-activation of B and T

cells during IM, B-cell immortalization, activation of pathogenic T cells, and cross-reactivity between EBNA-1-specific T cells and myelin antigens.[60] In addition, EBV-infected B cells in meningeal follicles and in perivascular spaces of blood vessels in white and/or gray matter of MS brains may induce a cytotoxic T lymphocyte response, consequently damaging surrounding tissues. However, EBV presence in brain or MS lesions is under dispute, with conflicting findings. Therefore, although it is possible that by modulating T-cell responses EBV impacts autoimmune reactions in MS, we are far from understanding the underlying mechanism through which this occurs.

Most epidemiological studies on EBV and MS were conducted in developed countries in the western hemisphere, and only very few in the developing world. Seroprevalence of EBV infections seems to be higher and to occur at an earlier age in developing countries,[61] thus explaining, at least in part, the lower incidence of MS in the region. In addition, there is evidence that regional EBV variants may differ from those observed in the US and Europe.[62] There are few reports on the link between EBV and MS in Latin America, with only one study from Mexico reporting no differences between MS and healthy controls in terms of the presence of EBV DNA in peripheral blood.[63] Thus, there is a considerable lack of information at the regional level regarding the relationship between EBV and MS. The fact that EBV variants seem to differ and that peak incidence occurs at a different age from other regions may provide new clues and deserves further exploration.

In addition to EBV, other infectious agents present during childhood and young adulthood have been implicated as potential participants in MS etiology. These include *Chlamydia pneumoniae*, a Gram-negative bacterium, although early enthusiasm over *C. pneumoniae* DNA and antibody presence in cerebrospinal fluid (CSF) of MS patients was not later confirmed.[64] Herpes virus-6 (HHV-6) is another example. Evidence of its involvement includes presence of viral DNA in MS autopsy tissue, increased viral DNA in blood cells during disease exacerbation, and higher IgG and IgM anti-HHV-6 antibody levels in the serum and CSF of MS patients. However, these findings do not explain immigration-related observations. Furthermore, viral DNA and anti-HHV-6 antibodies are also present in other neurological diseases, suggesting viral DNA or antigen detection might reflect HHV-6 reactivation from latency in peripheral blood T cells trafficking through the brain of patients with inflammatory central nervous system (CNS) diseases.[50,64]

Varicella zoster virus (VZV) is a neurotrophic virus that remains in the nervous system for decades. Although previous studies have postulated VZV as a possible candidate to participate in MS pathogenesis, results from most epidemiological or serological studies are insufficient to support an association between MS and VZV infection.[65] Recent Mexican studies linked progressive increase of MS incidence with increased VZV infection during childhood.[66,67] Interestingly, chickenpox during childhood is almost universal in endemic areas of MS, but far less common in areas of low MS prevalence, such as in tropical areas, where incidence is 50% of the general population.[66,68] In line with these observations, further studies from the same group recently reported large amounts of VZV DNA inside blood lymphocytes and CSF from MS patients during acute relapses, which vanished from the CSF in the same patients during remission. These findings support direct participation of VZV in MS etiology, possibly through host–virus interaction.[69] The authors also found VZV DNA in patients with progressive MS, but in low amounts.[69] Interestingly, DNA from other herpes viruses studied in MS patients, including HSV-1, HSV-2, EBV and HHV-6, showed no differences from control subjects.

The gut microbiome and dietary factors

Compelling evidence on the role of the microbiome in MS has largely emerged from animal models. Mice raised in a ''germ-free'' environment were highly resistant to developing experimental autoimmune encephalomyelitis (EAE), unless they had previously received a fecal transplant from mice colonized with gut microbiota.[70] Furthermore, reduced disease activity was observed in germ-free mice when EAE was induced, suggesting bacteria in the gut participate in activation of adaptive immune cells attacking the CNS. By contrast, certain bacterial strains exert a beneficial effect on EAE development and protect from disease exacerbation, suggesting different strains of bacteria which interact closely with the host immune system differ in their propensity to cause neuroinflammation.[71] Interestingly, there is evidence that risk factors for MS such as obesity, smoking, vitamin D deficiency/sunlight exposure and viral infections, also impact gut microbiota.[72] Human studies to support the role of microbiota in MS are scarce. Emerging cross-sectional, case-control studies have shown microbiota

composition differences between MS subjects and controls.[73,74]

Lately, the contribution of dietary habits to MS incidence and severity has come under scrutiny. Diet can exert direct effects on various cellular elements, and indirect ones through vascular risk factors. It can also influence the gut microbiome, resulting in changes in metabolism and immune function.[75] ''Western-style diets,'' characterized by high fat, cholesterol, sugar, and sodium chloride (NaCl) and a lack of fresh products, are believed to promote autoimmunity.[76,77] Excessive fat intake is in general a prominent factor; not only does it induce obesity, but a positive correlation between body mass index and risk of MS development, especially at younger ages, has also been observed.[78] Greater intake, as well as microbial production of long and medium-chain fatty acids, promotes differentiation of Th1 and Th17 myelin-reactive T cells, and suppresses Treg cell generation, exacerbating autoimmune responses in the CNS.[79] In line with these observations, intake of ω-6 polyunsaturated fatty acids (PUFAs), precursors of pro-inflammatory eiocosanoids, may promote Th17 pathway activation, increasing inflammation and negatively affecting immune homeostasis in the gut.[80] In contrast, recent work related ω-3 PUFAs to anti-inflammatory effects.[81,82] Furthermore, bacteria present in the colon ferment non-digestible carbohydrates, forming short-chain fatty acids (SCFAs) leading to expansion of protective regulatory T cells, ameliorating disease.[79,83] Likewise, butyrate, one of the SCFAs formed in the colon, modulates the immune response toward a non-inflammatory state by increasing IL-10 and IL-4 and inhibiting IFN-γ production from stimulated monocytes.[84]

Another typical hallmark of ''Western-style diets'' is high NaCl content. Two studies have shown that elevated NaCl concentrations promote CD4+ T-cell differentiation to Th17 cells. These experimental data correlated with in vivo observations in which high-salt diets accelerated onset and worsened clinical signs of EAE.[85,86] Based on these observations, our group recently demonstrated, in two independent cohorts of MS patients, a potential association between NaCl dietary intake, determined by urine excretion levels, and MS disease activity. Of note, serum NaCl remained relatively constant under different dietary conditions. Therefore, although association between increased salt intake and MS activity was demonstrated, causality could not be established based on these results.[87] Meanwhile, in a retrospective study investigating the association between salt intake and conversion of clinically isolated syndrome (CIS) to MS in patients receiving IFN-β1b, sequential 24-hour excretion levels were not associated with clinically definite conversion or MRI outcomes, suggesting salt intake does not influence MS activity.[88] Discrepancies between these results and ours may be explained by differences in: (1) patient selection (CIS vs. relapsing–remitting MS); (2) study design; and (3) genetic background, possibly impacting interaction between genetic and environmental factors in the context of sodium-induced CNS inflammation.

Although no long-term clinical trials currently exist, the findings discussed above clearly indicate that further investigation on the impact of dietary components, such as fatty acids and NaCl, on inflammatory processes is needed.

Based on these observations it is possible to speculate that Caucasian patients have different gut microbiota from Latin America patients. Undoubtedly, differences in population diets might favor the growth of particular microbial niches, which can either worsen or ameliorate the course of the disease. It is likely that studies on this topic will be conducted in different populations in the years ahead, the results of which might contribute to explaining differences in the incidence of MS in different regions.

Tobacco smoking

Cigarette smoking has been linked to an estimated 40–80% increased risk of developing MS in case-control studies.[89,90] Furthermore, smoking and MS risk have a dose-dependent relationship, since cumulative smoking reflected by cotinine serum or plasma levels is associated with increased risk. It is worth noting that this risk abates after a decade of smoking cessation.[91] Thus, adding smoking prevention or cessation to other treatment strategies would be a reliable and effective way to improve MS outcomes. Passive exposure to smoking has also been associated with increased MS risk, suggesting that lung irritation could trigger immune responses to CNS inflammation.[91] Interestingly, use of oral tobacco showed dose-dependent association with decreased risk of MS.[92] This observation supports the notion that lung inflammation itself drives the risk increase.

Tobacco smoking also impacts the clinical course of MS. Our group and others found cigarette smoking was a risk factor for early conversion to clinically definite MS among patients with CIS. Disease progressed more rapidly in ever-smokers compared with non-smokers. Moreover, MS patients who smoked

had a significantly higher risk of attaining Expanded Disability Status Scale score milestones (4 and 6) compared with non-smoker MS patients.[93,94] It is not clear whether increased impairment and disability in MS patients who smoke is due to the direct influence of tobacco on MS, or to increased co-morbidities. For example, cigarette smoking diminished anti-microbial activity relevant to airway infection clearance while simultaneously modulating mucosal functions, resulting in increased frequency of respiratory infections, both known to be important triggers of MS relapse.[95]

Smoking displays significant interaction with MS-associated HLA risk alleles. In Caucasian populations, having class II *HLA-DRB1*1501* or lacking *HLA-A*02* confers a significant increase in risk of developing MS, which is almost three times higher in smokers compared with non-smokers.[96] In addition, increased risk has also recently been associated to the N-acetyltransferase 1 (NAT1) *73688368* genotype, supporting genetic/environmental interactions in disease susceptibility.[97] As for most of the environmental factors described, studies in Latin America allowing a link to be established between smoking and MS susceptibility and/or clinical course are scarce. Hypothetically, differences may exist based on interactions between population-specific genetic factors and tobacco smoking. Observational and prospective studies in the region are of fundamental importance to confirm or rule out this association.

Conclusions and further perspectives

In recent years, an increasing number of lifestyle and environmental factors have been described as capable of augmenting susceptibility to develop MS, or impacting its clinical course.[98] In this review, only those extensively studied have been included. Others, such as early-life obesity, shift work, or assisted reproductive techniques have not been contemplated, but certainly require further investigation.

Unfortunately, very few studies linking lifestyle and environmental factors have been conducted in Latin American populations. Ethnic and geographical differences probably condition different responses to those observed in Caucasian populations, in which these factors have been analyzed extensively. Regional studies are warranted in the future to shed further light on these issues.

Conflicts of interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Correale is a board member of Merck-Serono Argentina, Biogen-Idec LATAM, and Merck-Serono LATAM, and Genzyme global. Dr Correale is a board member of Merck-Serono Argentina, Novartis Argentina, Genzyme LATAM, Genzyme global, Biogen-Idec LATAM, and Merck-Serono LATAM. He is part of the Steering Committee for the clinical trials of Ofatumumab (Novartis Global). Dr. Correale has received reimbursement for developing educational presentations for Merck-Serono Argentina, Merck-Serono LATAM, Biogen-Idec Argentina, Genzyme Argentina, Novartis Argentina, Novartis LATAM, Novartis Global, and TEVA Argentina as well as professional travel/accommodations stipends.
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Dr Gaitán has received reimbursement for developing educational presentations from Merck-Serono Argentina, Genzyme Argentina and Novartis Argentina, and travel/accommodation stipends from Biogen-Idec Argentina, Teva-Tuteur Argentina, Merck-Serono Argentina, and Novartis Argentina

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