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REVIEW

Association between seasonal factors and multiple sclerosis

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Abstract Multiple sclerosis (MS) is a chronic inflammatory disease that affects the central nervous system. MS is causing progressive and relapsing neurological disability, due to demyelination and axonal damage. The etiopathogenesis of MS is poorly understood. A number of environmental factors have been previously suggested, including: month of birth, vitamin D levels, smoking and viral infections. Previous studies assessing seasonal variation of relapses in multiple sclerosis have had conflicting results. The aim of this review is to assess the association between seasonal factors and MS, in terms of disease onset, relapses and activity.

Keywords Multiple sclerosis · Seasonality · Autoimmunity · Month of birth · Vitamin D · Melatonin · Environment

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Introduction

Multiple sclerosis (MS) is a T-cell mediated autoimmune disease, causing central nervous system (CNS) damage and a progressive decline in neurological function. The etiopathogenesis of MS is poorly understood, but it is widely accepted to be a multifactorial disease. A genome wide study reported in 2007 confirmed that HLA class II DRB1*1501 is associated with the disease, as well as two other genetic associations—to Interleukin-7 receptor-α chain (IL7RA 5p13) and interleukin-2 receptor-α chain (IL2RA 10p15) [1]; although the relatively low odds ratio for this association, as well as only 24 % concordance rate between monozygotic twins [2] suggest a crucial role of environmental factors in the development of MS.

A number of environmental factors have been suggested, including: month of birth, vitamin D levels, smoking and viral infections [3], but the most influential environmental factor that was found is geographic latitude—at birth and early adulthood [4, 5]. This gives rise to the hypothesis that climate, and perhaps seasonality, play an important role in the pathogenesis of MS.

The purpose of this review is to assess this association in terms of disease onset and activity, and to evaluate which season-dependent factors play a role in it (Table 1).

Month of birth

The effect of month of birth was first proposed in 1987, as a part of a study examining different neurological diseases. It suggests that those who were born in winter months have a reduced risk of developing MS, whilst people born in spring are at a higher risk [6]. An association between month of birth and MS was also found in a large-scale

Table 1 Studies on seasonal factors and multiple sclerosis

References	Design	Methods	Results
Willer et al. [7]	Population based study with population and family based controls and a retrospective cohort identified through death certificates	Data collection, 2 × 2 χ^2 test, McNemar's test, review of datasets	Association between month of birth and MS, stronger in familial cases
Ramagopalan et al. [8]	Case-control study	Patient and control recruitment, genotyped for HLA-DRB 1 genotype	A pronounced month of birth effect in MS patients with HLA-DRB1 genotype
Dobson et al. [11]	Meta-analysis and systematic review	Previously published data compared to expected birth rates, linear regression model	Month of birth effect was latitude dependent, and only significant in places that were >52°N
Fiddes et al. [14]	National statistics of 17 countries compared to expected month of birth distribution	Chi square test under the assumption of uniform birth rates in the population, to compare birth rates in different months	Association between MS and month of birth is probably false positive due to confounding variables
Ascherio et al. [20]	Randomized trial	Vitamin D levels of 468 patients were tested and compared between patients treated with interferon beta 1b early and late in the disease, and assessed for MRI findings—new lesions, lesions volume, MS relapses and disability	Low vitamin D levels early in the disease are a risk factor for long-term MS activity and progression
Munger et al. [22]	Analysis of data from 2 large cohorts	Assessment of diet at baseline and four years later	No association was found between vitamin D from food and MS incidence
Kampman et al. [24]	Observational study	Review article	A reduced incidence of MS in coastal fishing villages compared to inland farming areas
Panitch et al. [27]	Prospective study	Questionnaires used to evaluate symptoms of infections among patients and their immediate environment and MS attacks; also blood samples were tests for proof of infection	URIs of viral origin trigger MS attacks
Andersen et al. [33]	Prospective epidemiological study	60 MS patients followed for up to 31 months. URT and GI infections were recorded, with serological diagnosis of five common viral infections	Infections were associated with MS relapses (RR 1.3). A seasonal variation of the MS relapse rate was found minimum in summer
Tremlett et al. [34]	Prospective, population-based cohort	Prospective follow up for a mean 2.3. Associations between monthly ambient environmental factors, vitamin D, URT infections and relapse rates examined using weighted Pearson's correlation and linear regression	Relapse rates were inversely associated with UV and serum vitamin D levels and positively associated with URT infections
Edwards et al. [35]	Prospective cohort study	41 Patients documented all new symptoms of MS exacerbations and any intercurrent infections. Also monthly serum samples were taken for presence of antibodies against 6 viral infections, and Gd-DTPA enhanced MRI scans, during 15 months	Association was found between viral infections and MS exacerbations, the RR is even higher when viral infection is serologically confirmed
Constantinescu et al. [44]	Animal model	Mice were treated with luzindole, a melatonin receptor antagonist, and given immunization with spinal cord homogenate, to generate EAE	Treated mice did not develop EAE whereas control mice did
Farez et al. [45]	Prospective cohort study and animal model	Relapsing-remitting MS patients were tested for exacerbation rates, and melatonin levels (represented by melatonin metabolite g 6-sulfatoxymelatonin (6-SM)). Animal model used is EAE and assessed for disease symptoms and cytokines	Melatonin levels negatively correlate with multiple sclerosis relapses in humans, and melatonin treatment ameliorates pathology in a mouse model of multiple sclerosis

Table 1 continued

References	Design	Methods	Results
Kang et al. [46]	Animal model	EAE was induced in Lewis rats by immunization with rat spinal cord homogenates, and they were treated with 5 mg/kg oral melatonin	Melatonin significantly reduced the clinical severity of EAE paralysis ($p<0.01$), reduced spinal cord infiltration of inflammatory cells, reduced ICAM-1 immunoreactivity in the blood vessels of EAE lesions
Sandyk et al. [47]	Prospective cohort study	Nocturnal plasma melatonin levels, Plasma alpha-melanocyte stimulating hormone and the presence or absence of pineal calcification on CT scan was tested in a 25 MS inpatients	Abnormal melatonin levels were found in 13 patients (52.0 %), 11 of whom had nocturnal levels which were below the daytime values. There was a positive correlation with age of onset of symptoms ($p < .0001$) and an inverse correlation with the duration of illness ($p < .05$).
Jin et al. [49]	Meta-analysis	Weighted information was obtained from 9 reports on monosymptomatic optic neuritis, 6 reports on MS onsets and 9 reports on MS exacerbations	Monosymptomatic optic neuritis, MS onsets and MS exacerbations in the Northern hemisphere present a similar pattern with highest frequencies in spring and lowest in winter
Spelman et al. [50]	Prospective epidemiological study	Data from a registry were utilized to analyze seasonal relapse onset distribution by hemisphere and latitudinal location. A sine regression model was used to model relapse onset and UVR seasonality. Linear regression was used to investigate associations of latitude and lag between UVR trough and subsequent relapse peak	Relapse onset followed an annual cyclical sinusoidal pattern with peaks in early spring and troughs in autumn in both hemispheres. Every 10° of latitude away from the equator was associated with a mean decrease in UVR trough to subsequent relapse peak lag of 28.5 days (95 % CI 3.29–53.71, $p = 0.028$)
Simpson et al. [52]	Prospective cohort study	145 participants with relapsing-remitting MS were followed from 2002 to 2005. Serum vitamin D levels were measured biannually, and the hazard of relapse was assessed using survival analysis	Higher 25-OH-D levels were associated with a reduced hazard of relapse
Lucas et al. [53]	Multicenter case-control study	216 cases and 395 age and sex matched controls from Australia (latitudes 27°S to 43°S), between 2003 and 2006. Exposures measured included self-reported sun exposure by life stage, objective measures of skin phenotype and actinic damage, and vitamin D status	Higher levels of past, recent, and accumulated leisure-time sun exposure were each associated with reduced risk of first demyelination event. Higher serum vitamin D status was also associated with this risk
Auer et al. [54]	Retrospective study	MRI scans from 53 untreated MS patients were analyzed, and patients were followed to document monthly rate of active scans and the average number of enhancing lesions per month	Biphasic seasonal fluctuation of the disease activity was found, which was highest in spring and early summer and lowest in autumn. The number of active lesions was significantly higher in the first half of the year
Killestein et al. [56]	Analysis of data from another multicenter, randomized, double-blind, placebo-controlled study	Cohort of 13 untreated MS patients for 9 months. Assed for clinical disease activity, monthly MRI, and blood was taken for immune measurements	Disease activity (measured by active MRI lesions) is associated with a significant transient decrease in both T cells producing interferon-γ
Meier et al. [57]	Observational cohort study	Disease activity was assessed from lesions on 939 separate brain T2 MRI scans of 44 untreated MS patients. Both likelihood and intensity of disease activity were compared with the time of year and regional climate data. Contrast-enhancing lesions and attack counts were also compared for seasonal effects	New T2 activity revealed a likelihood 2–3 times higher in March–August than during the rest of the year, and correlated strongly with regional climate data. Disease intensity was elevated during the summer season

Table 1 continued

References	Design	Methods	Results
Mowry et al. [58]	Longitudinal cohort study	A 5-year cohort in which 469 participants had clinical evaluations, brain MRI, and blood draws annually. Analyses preformed, and annual 25-hydroxyvitamin D levels were evaluated for their association with subsequent new T2-weighted and gadolinium-enhancing T1-weighted lesions on brain MRI, clinical relapses, and disability	Vitamin D levels are inversely associated with MS activity on brain MRI
Zivadinov et al. [59]	Data obtained from another ongoing prospective study	264 subjects underwent neurological MRI examinations, provided blood samples and answered questions to a structured questionnaire. Information on race, skin and eye color, supplement use, BMI and sun exposure was obtained by questionnaire. 25-hydroxy vitamin D3, 1, 25-dihydroxy vitamin D3 and 24, 25-dihydroxy vitamin D3 levels were measured	Increased summer sun exposure was associated with increased grey matter volume and whole brain volume after correcting for EDSS. Inclusion of 25-hydroxy vitamin D3 levels did not substantially affect the positive associations of sun exposure with white and grey matter volume
Stewart et al. [61]	Case-control study	Levels of IFNγ, TNFα, Il-4 and Il-10 produced by mitogen-stimulated peripheral blood mononuclear cells were measured in relapse/ remitting MS patients and controls. Blood was taken in summer and winter	Controls had a summer excess of Il-4, Il-10 and TNFα, and a winter excess of IFNγ. Untreated MS cases had a summer excess of Il-10, whereas those treated with Interferon-beta had lower levels of all cytokines, and displayed no seasonal effect
Mahon et al. [62]	Randomized, double-blind, placebo-controlled study	MS subject divided in two groups: controls received 800 mg supplemental ca, and vitamin D treated received 800 mg supplemental Ca + 1000 IU vitamin D, daily for 6 months. Blood samples were collected for both serum and peripheral blood mononuclear cell(PBMC) isolation	Vitamin D supplementation significantly increased serum TGF-β1 levels 6 months later. Placebo treatment had no effect on serum TGF-β1 levels. TNF-α, IFN-γ, IL-13 were not different following supplementation

population based study conducted in 2005; the association was stronger in familial cases of MS, indicating a possible epigenetic influence during gestation [7]. This finding was supported by a case-control study, that found the effect of month of birth to be a more pronounced in MS patients with HLA-DRB1 genotype [8]. The month of birth also had an effect on the phenotype of the disease (primary progressive MS vs relapsing–remitting MS) [9].

It has been hypothesized that low maternal vitamin D levels, due to reduced sun exposure in the winter months, plays a significant role in this phenomenon. Reduced vitamin D levels may affect the immunological development of the fetus in a critical time during pregnancy, resulting in an increased risk of MS [10]. A recent meta-analysis and systematic review found that the month of birth effect was latitude dependent, and only significant in places that were over 52°N [11]. It was previously suggested that at this latitude, insufficient ultraviolet B (UVB) radiation reaches the skin between October and March, leading to inadequate vitamin D synthesis during this time [12, 13]. One significant limitation of the previously discussed meta-analysis was that it only included studies in the northern hemisphere. Demonstration of an inverse relationship between month of birth and MS risk in similar latitudes of the southern hemisphere would significantly strengthen its conclusion [11].

If the month of birth effect is related to maternal vitamin D levels as mentioned above, it is plausible that the effect would be eliminated by the use of vitamin D supplementation during pregnancy. A retrospective study is needed to investigate the impact of maternal vitamin D supplementation the effect of the month of birth on MS incidence, and to establish the underlying mechanism. This could potentially lead to the use of antenatal vitamin D supplementation in those with a strong family history of MS, as the effect of month of birth is strongest in familial cases [8].

Whilst maternal vitamin D levels are the most widely accepted explanation of the month of birth effect, other factors that may play a role, include: perinatal infections, climate and variations in lifestyle.

Not all investigators agree with this conclusion. A study by Fiddes et al. [14] suggests that the association between MS and the month of birth is only mediated by several confounding variables, such a year and place of birth.

Vitamin D levels

Vitamin D is synthesized in the human body on response to exposure to sunlight, and specifically UV radiation [15]; therefore, it is easy to infer that vitamin D levels are higher during the summer months, as mentioned above [13].

Vitamin D has been previously associated with numerous autoimmune diseases, such as systemic lupus erythematosus, type I diabetes, inflammatory bowel diseases, rheumatoid arthritis, and of course, with MS [16–19].

The BENEFIT trial showed an inverse relationship between vitamin D levels and MS disease activity, progression, new active lesions, yearly increase in T2 lesion volume and yearly loss in brain volume. This study was performed in patients presenting with their first MS event, although the safety and efficacy of vitamin D therapy for relapsing remitting MS patients is still under clinical trial [20, 21]. Similar results, in regard to low levels of vitamin D and high disease activity and progression were found in another study [20]. Munger et al. [22] have demonstrated a protective effect of vitamin D intake on the risk for developing MS. Norway has low UV radiation exposure, since its latitude is 58°–71°N, which should expose its residence to high risk for MS. In a research done there, reduced incidence of MS was found in coastal fishing villages compared to inland farming areas. The interpretation of this finding was based on the assumption that coastal inhabitants have increased dietary vitamin D intake [23, 24]. This shows that dietary vitamin D can modulate the latitude-dependent risk of MS in areas with low exposure to the sunlight.

It could be concluded that vitamin D plays a crucial role as a seasonal factor of MS, although it seems that the seasonality effect could not be attributed to vitamin D alone.

Infections

Many infectious diseases have seasonal pattern of outbreaks [25, 26]; these patterns are due to seasonal changes in both the pathogens and in the host [26].

Infections have been noted to increase levels of cytokine IFN-γ [27, 28], which has a significant role in MS disease exacerbation [29–31]. Sibley et al. showed minor infections, particularly those of viral origin, frequently encountered in the winter, precipitated disease exacerbation. Nearly 30 % of MS attacks were associated with either preceding or concurrent infection. Infections were mainly of the upper respiratory and gastrointestinal systems, although no particularly antigen was isolated. Bacterial infections, in particular urinary tract infections, were not significantly documented as a disease trigger [32]. Other investigators have demonstrated the relationship between infection and exacerbation since [33–35].

Edwards et al. [35] detected a significant increase in the volume of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) enhancing lesions in MRI scans at the time of serologically confirmed viral infections compared to non-infection periods. The area and volume of Gd-DPTA enhancing lesions has been associated with MS disease exacerbation although the quantitation of such lesions remains undetermined [35–38]. Such findings suggest a positive connection between viral infection and MRI evidence of the destruction of the blood-brain-barrier. This could result from a viral-induced inflammatory response affecting the CNS [35].

Melatonin

Melatonin is a hormone made in the pineal gland, and it is responsible for the circadian rhythms of physiological functions. Its secretion changes according to daylight time and night length, and therefore, it changes with the seasons [39]. In recent years, there is increasing evidence that Melatonin has a great influence on the immune system, and more specifically, it seems to enhance the release of T-helper type 1 (Th1) cytokines, and might also influence Th2 cells [40, 41]. Melatonin's influence on the pathogenesis of autoimmune diseases in general, and of MS in particular, is still controversial [42]. Polymorphisms in genes related to the melatonin pathways were found to be associated with progressive subtypes and higher disability status in Finnish MS patients [43]. Evidence for the role of melatonin as an immunologic enhancer, and its adverse effect on MS can also be found in a study that tested the impact of treatment with luzindole, a melatonin receptor antagonist; Luzindole treatment prevented the development of experimental autoimmune encephalomyelitis (EAE) in mice [44].

Evidence for the ameliorating effect of melatonin on MS can be found in a study by Farez et al. [45] in which investigators showed melatonin levels were inversely correlated with MS relapses in humans. In animal models of

EAE, it was shown that melatonin treatment could improve the disease's clinical symptoms. In another study, investigators demonstrated that oral administration of melatonin reduced the clinical severity and spinal cord inflammatory infiltration in mice with EAE [46].

Sandyk et al. investigated the association between nocturnal melatonin levels and the presence of pineal gland calcification during MS exacerbations. Abnormal melatonin levels, mostly low nocturnal levels, were found in 52.0 % of patients. Melatonin levels were found to be positively correlated with the age of onset of symptoms of the disease ($p < 0.0001$) and negatively correlated with the disease's duration ($p < 0.05$). Pineal gland calcification was found in 96 % of subjects, suggesting a possible role of pineal failure in the disease [47].

Thereby, melatonin could be one of the factors that mediated the association between MS and seasonality, and its role in the disease should be studied further.

Seasonality and disease activity

Previous studies have demonstrated seasonal variations in disease activity (Table 1). These variations have been investigated using three main parameters of disease activity: clinical relapses, magnetic resonance imaging (MRI) findings and immunoregulatory cytokine production.

Seasonality and clinical MS relapses

Several studies have examined the seasonal variation in relapse rates, and have reported conflicting results. In 2000, Jin et al. performed a meta-analysis examining the relationship between season and mono-symptomatic optic neuritis (a known symptom of MS [48]), MS onset and MS exacerbations. The researchers concluded that there is a peak in incidence during spring and a nadir during winter months in the northern hemisphere in all three parameters, which was highest with respect to MS onset (45 % with 95 % CI 36–55 %), and lowest with respect to its relapses (10 % with 95 % CI 7–13 %) [49]. A large, global multicenter study conducted in 2014 by Spelman et al. further demonstrated a latitude dependent effect. This study involved 8411 patients in 31 centers in the northern hemisphere, and 1400 patients in 15 centers in the southern one, with a total of 32,762 MS relapses analyzed. They found a significant difference of 7.62 % between peak and trough relapse difference per 100 patients, and the mean lag time between UV radiation trough and relapse onset peak was 2.72 months, for both northern and southern hemispheres. The relationship between lag time and latitude was also assessed, and it was found that with each change of 10° in latitude (away from the equator) the lag time was reduced by a mean of 28.5 days [50].

The variation according to latitude may be mediated through the UVR exposure, and its immunomodulatory effect and it is most likely due to vitamin D synthesis. However, this raises concerns because does not fully explain the high rate of exacerbations during the spring months, as vitamin D levels are lowest during winter time [13]. Inhabitants of countries further from the equator are known to have lower vitamin D levels in general [51], and thus are more likely to reach a vitamin D deficiency sooner after the UVR deprivation. In 2010, Simpson et al. reported an inverse relationship between vitamin D status and the likelihood of MS relapse [52]. An Australian study concluded that vitamin D levels and sun exposure are independent risk factors for CNS demyelination [53].

Seasonality and brain lesions in MRI

MRI is a useful technique to evaluate the effect of seasonal factors on MS, as it is an objective measure of sub-clinical disease activity in the CNS. Unfortunately, its use is limited by its high cost and therefore studies using MRI data are scant and typically have small sample sizes.

In 2000, Auer et al. [54] demonstrated a sinusoidal variation in the number of new contrast enhancing lesions (CEL), similar to the patterns described in clinical relapse rates. However, two studies published the following year independently concluded that no seasonal variation was observed using MRI, one followed 120 MS patients for 10 months while the other followed 13 patients for 9 months [55, 56]. The lack of an acceptable inclusion criteria and poor longitudinal follow up has cast doubt over the validity of the results of previous studies.

More recently, an observational cohort study concluded that there was a strong seasonal pattern of MS activity observed using non-contrast brain MRI. Although only 44 patients were included, its design and control for confounding variables, such as treatment, strengthened its validity. A total of 939 scans were used, with a median of 22 scans per patient, and it concluded there was a two-three-fold increase in likelihood of new lesions as well as increased disease activity during the spring-summer months [57].

Mowry et al. [58] reached a conclusion that vitamin D levels are inversely associated with MS activity on brain MRI, using scans of 469 subjects, and suggested this could possibly explain the effect of seasonality. Zivadinov et al. used MRI scans, serum vitamin D metabolite levels and questionnaires of 264 MS patients in order to explore the relationship between sun exposure, vitamin D and MRI documented disease activity. They concluded that sun exposure has a direct effect on MRI measures of

neurodegeneration (measured by changes in brain volume and grey matter volume), independently of vitamin D levels [59]. Although this study does not examine seasonal variation of vitamin D or UVR, but rather sun exposure throughout the patient's life, we have included it in this review, as it demonstrates the existence of an effect of UVR that is not mediated by vitamin D, and thus highlights a need for further research in order to identify this factor.

Seasonality and immunoregulatory cytokines

The CNS damage and progressive neurological decline characteristic of MS is thought to be mediated by the Th1 immune response, of which interferon γ (IFN-γ) is the hallmark cytokine. Levels of IFN-γ are naturally elevated during the inflammatory process of the nervous system via Interleukin-12 (IL-12), a pro-inflammatory cytokine. The CD40–CD40 ligand interaction between antigen presenting cells and T-cells leads to production of IL-12 and subsequently secretion of IFN-γ. IFN-γ and IL-12 are both also released by peripheral blood mononuclear (PBMN) cells [29]. In progressive MS patients, increased levels of IFN-γ have been found to precede clinical attacks and treatment of these patients with recombinant IFN-γ induces disease exacerbation [29–31].

Balashov et al. studied the relationship between levels of immunoregulatory cytokines in progressive MS patients and the time of year. They, amongst other studies such as Killestein et al., found significantly increased IFN-γ production in these patients during autumn and winter months when compared to spring and summer months, as well as when compared to IFN-γ levels of healthy patients during autumn and winter months [29, 30]. The apex of these increased levels occurred from October to December. Expanded Disability Status Scale (EDSS—validated evaluation of neurologic impairment in MS [60]) scores of progressive MS patients seen during this period worsened by 0.03 more compared to those patients seen during the March to August period. IL-12 was studied as well to determine its role in IFN-γ secretion. With neutralization of IL-12, IFN-γ production significantly decreased in progressive MS patients during the winter and autumn months. There was no change in IFN-γ levels with IL-12 neutralization during the spring and summer months for progressive MS patients or for healthy controls [29].

Although the mechanism for this seasonal effect is unknown, it is suggested that environmental factors, such as UVR, act as the inciting causes for disease onset and exacerbation. UVR exposure is positively correlated to vitamin D activation, and vitamin D inhibits IFN-γ -therefore increased UVR exposure leads to decreased IFN-γ levels [29, 61]. Vitamin D supplementation was also previously associated with increased levels of transforming growth factor beta 1 (TGF-β1) [62].

Conclusion

MS is an autoimmune multifactorial disease whose outbreak and course are influenced by genetic and environmental factors. One important environmental factor is seasonality. The effect of seasonality itself could be explained by various factors, including vitamin D levels, melatonin, infectious diseases and the month of birth, which is most widely explained by maternal vitamin D levels as described above.

Seasonal variation on MS disease's course has been demonstrated in various studies, and seems to have an effect on clinical manifestations of the disease, MRI brain lesions, and inflammatory cytokine levels.

Low vitamin D levels are associated to most, but not all of the environmental factors mentioned. This review article supports the theory, past research and present research of vitamin D as an immunomodulator in MS, but also of seasonality as an independent factor in the disease.

Compliance with ethical standards

Conflict of interest None.

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