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Review

Environmental triggers of multiple sclerosis

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ABSTRACT

Multiple sclerosis is a chronic immune-mediated disease of the central nervous system that develops in young adults with a complex genetic predisposition. Similar to other autoimmune disease, HLA-DR and -DQ alleles within the HLA class II region on chromosome 6p21 are by far the strongest risk-conferring genes. Less robust susceptibility effects have been reported for non-MHC related genetic variants. Improvements in the design of epidemiological studies helped to identify consistent environmental risk-associations such as the increased susceptibility for MS in individuals with a history of infectious mononucleosis, a symptomatic primary infection with the human γ-herpesvirus Epstein–Barr virus (EBV). Sun exposure and serum vitamin D levels are emerging non-infectious environmental risk factors that may have independent roles. The analysis of environmental effects will likely expand in the next few years and will allow for the generation of testable hypotheses as to how environmental insults interact with genetic factors to jointly determine the susceptibility to MS. Insights gained from these studies might facilitate the development of prevention strategies and more effective treatments for MS.

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS) characterized by chronic inflammation, demyelination, gliosis, and axonal pathology. Similar to other common autoimmune diseases, predisposition to MS is conveyed by immune system associated genes, the strongest risk factor, HLA-DRB1*1501, being encoded in the class II major histocompatibility (MHC) genomic region [1]. Nevertheless, the high discordance rate among monozygotic twins as well as the multitude of migration and epidemiological studies that show latitude-dependent north to south gradient of increasing disease incidence (in the northern hemisphere and the opposite in the southern) and remarkable differences in risk among people of common ancestry who migrate to areas of low or high MS prevalence [2], indicate that MS is a complex multifactorial disease that results from the intricate, yet not well-understood, interaction of both genetic and environmental factors.

The quest for identification of the potential environmental triggers of MS has been ongoing for decades. Both infectious and non-infectious agents have been implicated as potential culprits. This review aims to discuss the environmental factors that have attracted the most attention in the recent years, including viral infections, vitamin D, and smoking. Yet, the plethora of controversy in the field makes it difficult to discern one single environmental factor as a sole trigger of MS. Rather it is more likely that MS susceptibility is dependent on the elaborate interaction of a variety of low penetrance genetic factors and environmental agents conveying by themselves low risk, but when combined together resulting in disease initiation.

2. Genetic factors

Familial aggregation studies consistently showed that the risk of developing MS is higher for people with MS in the family and related to the number of genes that are shared with family members diagnosed with MS. For instance, a monozygotic twin of an MS patient has more than 100 times higher risk, compared to the general population, to develop the disease, while a full-sibling will have only 20 times and half-siblings only 10 times higher disease risk [3,4]. Notably, the relationship between familial recurrence risk and genetic relatedness is non-linear, suggesting that the susceptibility to develop MS is determined by multiple risk alleles, each with modest individual effects.

Genome-wide association studies (GWAS) have proved to be a powerful tool for identifying particular genetic variants associated with complex diseases and traits. So far, seven GWAS have been conducted involving almost 10,000 MS patients and 15,000 controls and investigating more than 100,000 single nucleotide polymorphisms (SNPs). For more than 3 decades, the MHC class II region on chromosome 6p21 was the only known MS risk locus.

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GWAS identified HLA-DRB1*1501 as the main susceptibility allele for MS with an odds ratio of 2–3. Other yet less robust susceptibility effects were found for other risk loci such as *IL7R* [5]. Surprisingly, other MS-associated loci like *IL2RA*, *CLEC16*, and *CD226* are also know to play role in susceptibility to other autoimmune disease such as Type 1 diabetes [6]. This overlapping association points at common defects in essential immune system pathways that initiate development of autoimmune pathologies. However, all of these newly identified MS risk alleles have minor individual effects with odds ratios lower than 1.3. Moreover, the distinction whether these susceptibility variants have causative effect or are inherited due to strong linkage disequilibrium with other yet unidentified causal variants remains elusive as so far we do not understand their functional contribution to MS development.

Although a simple discordance rate might not accurately reflect the contribution of non-genetic or environmental factors since experimental studies in congenic mice with gradually increasing numbers of lupus-associated genes have shown that the rate of disease expression can be titrated through the number of disease-linked genes under identical environmental influences [7], the high discordance rate in monozygotic twins along with changes in risk that occur with migration indicate that environmental agents play an essential role in the development of MS.

3. Infectious environmental factors

From the very early days of MS discovery, infections have been proposed to be the underlying causes of disease initiation. This assumption led to the development of the first FDA-approved immunomodulatory treatment for MS, Interferon-beta (IFN-b), known for its antiviral activities. Pierre Marie, a former student of Jean-Martin Charcot, who first described multiple sclerosis as a clinical entity in 1868 [8], strongly argued that infectious pathogens, or more likely combined infections, initiate MS [9]. This hypothesis was formed during the "golden era" of microbiology and most likely driven by the excitement over remarkable breakthroughs in the causes and preventions of many infectious diseases by researches like Louis Pasteur and Robert Koch. A long list of potential infectious triggers of MS has been investigated since then. The ones that have received most attention during the past years are discussed below.

4. Epstein–Barr virus

Among the large list of proposed pathogens, including various herpesviruses, varicella zoster virus, human endogenous retroviruses, Torque teno virus, Chlamydia and other bacterial agents, Epstein–Barr virus (EBV) has gained the most notable scientific interest to date. In the industrialized world, about 50% of the population acquires EBV between 1 and 5 years of age, while another large percentage contracts the virus during adolescence [10]. For about 30–50% of individuals who acquire the virus in the second decade or later in life, the virus would lead to symptomatic primary infection known as infectious mononucleosis (IM) that is characterized by glandular fever and massive expansion of virus-specific T lymphocytes that subside with the resolving of the infection [10]. Due to improvement of sanitary conditions in the developed world, it is becoming more common for individuals to acquire EBV late in life.

Interestingly, compelling evidence support the association of IM with elevated risk of MS occurrence [11–14]. Based on a recent updated meta-analysis evaluating a total of 18 clinical studies, the combined relative risk for development of MS after IM was estimated at 2.17 (95% CI 1.97–2.39; $P < 10^{-54}$) [15], while when analyzed in HLA-DRB1*15 carriers individuals with history of IM had a sevenfold increased risk of developing the disease [16].

A multitude of epidemiological studies conducted in the past 30 years revealed that MS patients are almost universally, 99.5%, seropositive for EBV infection, compared to matched healthy controls who have EBV seroprevalence of 94.2% [17]. This difference in seropositivity is even more pronounced in pediatric MS cases which have been shown to carry 83% seroprevalence compared to only 42% in matched healthy controls, while no significant difference was observed for other viruses such as CMV, parvovirus B19 and varicella zoster [18]. Even though, these observations suggest that EBV plays a role in MS predispositions, EBV infection is not a prerequisite for disease development since a substantial fraction of children with MS is seronegative for EBV.

Levin et al. investigated blood samples from more than 3 million US military personnel taken in continuation of 12 years [19]. The study investigators identified 69 MS cases and compared them to matched controls and estimated that a fourfold elevation in antibodies specific for a mixture of EBV nuclear antigens (EBNA) was associated with a threefold increase in risk of developing MS. No such association was observed for CMV antibody titers. EBNA-specific antibodies in individuals who developed MS did not differ significantly from healthy controls before reaching the age of 20, while EBNA1 antibodies were two to threefold elevated in MS individuals at the age of 25 or older suggesting an age-dependent alteration in EBV-specific antibody titers. No correlation between the age nor the severity of IM infection and MS risk could be found [20,21]. Levin et al. speculated that the observed changes in EBV immunity could be due to concomitant infection with other microorganisms or possibly with distinct strains of EBV that alters immune responses to the virus and lead to higher risk of MS.

Similar observations were made by DeLorenze et al. who investigated serum samples of MS patients up to 30 years before disease onset and determined a significant increase in EBNA1-specific IgG titers compared to matched controls, which occurred 15–20 years prior to disease onset [23]. In patients with clinically isolated syndromes (CIS), antibody responses towards EBNA1 were shown to be elevated compared to healthy EBV carriers and were predictive for conversion to clinically definite MS [24].

Pediatric MS patients were also observed to have increased and broadened recognition of EBV-encoded nuclear antigen-1 (EBNA1) antibodies, pointing at an early dysregulation of virus-specific immune control [25].

EBNA1 is the only EBV-encoded antigen that is consistently expressed in proliferating EBV-infected memory B cells and $CD4^+$ T lymphocytes are thought to play an important role in the immune control of persistent EBV infection. While healthy EBV-carriers preferentially recognize multiple epitopes within the central part of the immunogenic domain of EBNA1, MS patients have been shown to have significantly elevated EBNA1-specific $CD4^+$ T cell frequencies targeting a much larger number of epitopes within this region [26]. EBNA1-specific $CD4^+$ T lymphocytes, but not T cell specific for other lytic or latent EBV and CMV peptides, were observed to have a higher proliferative capacity and enhanced IFNγ secretion.

It is tempting to hypothesize that molecular mimicry enables EBNA1-specific T cells to cross-recognize self-autoantigens that would eventually lead to the initiation and maintenance of autoimmune pathologies. In support of this hypothesis, one study showed that MS patients present with selective elevation of EBNA1-specific T cells response that recognize more frequently myelin antigen than other non-MS-associated autoantigens [27].

Another hypothetical mechanism of how EBV could trigger autoimmunity is based on its ability to infect and immortalize B cells by mimicking T-cell help and B-cell receptor signaling [28]. Therefore, it is tempting to speculate that EBV could potentially infect and immortalize autoreactive B cells that contribute to disease pathology. Interestingly, the importance of B cells in MS has

gained increasing recognition and currently numerous agents either depleting or interfering with B-cell differentiation are being tested for their potential efficacy in MS treatment. Moreover, a study by Serafini et al. reported that postmortem MS brain samples, but not samples from patients with other inflammatory CNS disease contained considerable numbers of EBV-infected B cells expressing viral antigens [29]. However, the observations from this study could not be reproduced by others [30–32].

In conclusion, there is strong epidemiological evidence linking symptomatic EBV infection with MS development rendering the virus a major candidate for MS initiation. However, further experiments are needed to elucidate the exact molecular mechanisms that lead to this association.

5. Human herpesvirus-6

Another ubiquitous herpesvirus that has gained relative popularity as potentially associated with MS is the human herpesvirus-6 (HHV-6). It is characterized by phases of latency and reactivation that bear similarity to relapsing-remitting MS. The virus has neurotropic potential and was reported to infect oligodendrocytes and microglia cells [33], as well as to establish latency in CNS tissue which serves as a reservoir of persistent infection [34]. Another aspect that strengthens the hypothesized involvement of the virus in MS is the observation that primary HHV-6 infection may lead to severe neurological complications such as encephalitis and epilepsy. Besides being able to infect neural cell, HHV-6 most commonly establishes infection in T lymphocytes and supposedly exerts modulatory effects on the immune system [35].

Various studies in the past 15 years have investigated HHV-6 association with MS. HHV-6 has been detected in serum, CSF as well as in brain tissue and more predominantly in MS lesions as reported by some studies [36], [37,38], yet contradicted by others [39].

Besides direct cytopathic effect, other putative mechanisms of HHV-6 involvement in MS pathology include bystander activation, and molecular mimicry. The later of which has gained compelling evidence. Myelin basic protein (MBP), a suspected target of autoreactivity in MS, has been determined to share sequence homology with HHV-6-encoded U24 protein. Cross-reactive T cells responding both to MBP and U24 peptides were elevated in MS patients compared to controls [40].

So far, there is no epidemiological evidence that symptomatic HHV-6 infection increases the risk for development of MS [41] and there is no data that would unequivocally support an etiologic role of HHV-6 in the pathogenesis of MS. However, the neuro- and lymphotropic potential of virus suggests that bystander reactivation of HHV-6 could potentially augment CNS inflammation.

6. Varicella-zoster virus

Varicella-zoster virus (VZV) is a ubiquitous pathogen that establishes latency in the dorsal ganglia in about 95% of adults [42]. It is the causative agent of varicella (chickenpox), and can occasionally lead to symptomatic reactivation known as zoster [43]. Numerous epidemiological studies have investigated the link between VZV and MS, nevertheless, a meta-analysis including 40 reports conducted between 1965-1999 revealed that there is insufficient evidence to support such association [44]. Presence of VZV DNA, however, has been reported in blood cells [45] and CSF [46] from relapsing MS patients. Furthermore, Sotelo et al. observed electron microscopically abundance of viral particles identical to VZV in the CSF of MS patients during the initial days of disease relapse [47]. However, when Burgoon et al. used identical electron microscopic and PCR techniques they failed to identify presence of viral particles or DNA in MS CSF or acute MS plaques [48].

The weak epidemiological data and the inconsistency in the observations render the link between VZV and MS elusive.

7. Torque teno virus

Sospedra et al. determined the specificity of clonally expanded T cells from CSF of MS patients during exacerbation and observed that these T cell clones recognized evolutionary conserved arginine-rich motifs of functional protein domains of the orphan virus Torque teno virus (TTV) [49]. T cell clones resounded to TTV peptides as well as to peptides from other common viruses and self-antigens. Therefore, the authors speculated that repeated encounter, both of pathogenic or non-pathogenic infectious agents can lead to expansion of T cells responsive to conserved protein domains that are able to cross-react with ubiquitous self-antigens. These observations allude to the conclusion that recurrent infections with multitude of ubiquitous pathogens rather than one particular infectious agent could be implicated in the initiation of reactivity towards self-antigens that may trigger autoimmune pathologies. However, due to the paucity of data, the relation of TTV infection and MS remains ill defined.

Not only viruses and bacteria have been linked to MS, but also parasites. Helminthes are thought to have a protective role in MS among other autoimmune diseases [50]. The prevalence of helminth infections in countries with high sanitation standards has lead to the proposition of the hygiene hypothesis stating that regular exposure to various pathogens is required for the development of appropriate immune responses. Administration of helminthes has been shown to ameliorate disease in a mouse model of MS [51,52]; while one clinical study has shown that when MS patients developed asymptomatic gastrointestinal infection, they experienced reduction of clinical and radiological MS activity, characterized by downmodulation of proinflammatory cytokines and increase in IL-10 and TGF-β production [53]. The role of helminthes in MS is more extensively discussed in an excellent review by Fleming [54].

8. Non-infectious environmental factors

8.1. Vitamin D

Among the non-infectious environmental triggers, there is a recent upsurge in studies investigating the effects of vitamin D levels on MS pathogenesis. Vitamin D is a potent immunomodulator affecting proinflammatory pathways [55,56] as well as the number and activity of regulatory T cells [57]. Epidemiological studies have shown an increase in MS frequency with increasing distance from the equator, which inversely correlates with duration and intensity of sunlight [58–62]. Interestingly, populations situated at high latitudes but having high consumption of vitamin D rich food were observed to have reduced MS prevalence [63–65], while the risk of MS incidence decreased with movement from high to low altitudes [2].

Timing of birth has also been implicated as a predictor of MS susceptibility. A study including a large data set of more than 40 000 MS patients from Sweden, Denmark, Canada and Great Britain revealed that significantly fewer individuals with MS were born in November, while the incidence of MS was significantly higher for people born in May, indicating an association between prenatal sunlight and risk of MS. Interestingly, the effect of month of birth was more evident for familial cases, suggesting a potential gene/environment interaction [66].

In order to investigate the contribution of childhood sun exposure Islam et al. compared sun exposure-related childhood activities of 79 MS-discordant monozygotic twin pairs [67]. Their observations confirmed the disease protective effect of sunlight. Lucas et al. investigated whether past and recent sun exposure using self-report questionnaires and objective measures of vitamin D levels are associated with risk of first demyelinating event (FDE) in Australia [68]. They found that higher levels of past, recent, and accumulated leisure-time sun exposure were each associated with reduced risk of FDE and that higher serum 25-hydroxyvitamin D [25(OH)D] levels were independently associated with decreased FDE risk. Some of the aforementioned interpretations should be made with caution since, similar to all other questionnaire-based studies, these results are subjected to recall bias.

To date there is only one longitudinal prospective, nested case-control study that investigated serum samples from more than 7 million US military personnel and revealed that high serum levels of 25(OH)D, the metabolite routinely used to evaluate an individual's nutritional vitamin D status, are associated with reduced incidence of MS [69].

Moreover, seasonal variations in vitamin D levels inversely correlated with gadolinium-enhancing magnetic resonance imaging lesions [70] and relapse rate [71–74]. In a study investigating serum samples from 267 MS patients, Smolders et al. observed association of low vitamin D levels with both relapse and degree of disability as measured by EDSS (Expanded Disability Status Scale)-scoring [75].

In order to investigate better the 25(OH)D availability to the brain, Holmøy et al. measured 25(OH)D levels in CSF and found that CSF levels positively correlate with serum vitamin D concentrations. However, they could not find any significant difference between the levels of the biologically active vitamin D metabolite, 1,25(OH)D in MS patients and controls as well as no association with relapse or gadolinium-enhanced lesions was determined [76].

An explanation for the beneficial effects of elevated vitamin D levels could lie in the immunomodulatory potential of the vitamin. It has been shown to affect and tolerize DCs by suppressing their pro-inflammatory cytokine secretion, expression of maturation markers, chemotaxis, and capacity to trigger proliferation of antigen-specific T cells, therefore indirectly inhibiting potentially autoreactive T cells [77].

Furthermore, since T cells themselves are described to carry vitamin D receptors (VDR), direct T cell inhibition is another hypothesized molecular mechanism of vitamin D effect on MS pathology. A recent study conducted in mice model of MS reported that 1,25(OH)D directly inhibits autoreactive T lymphocytes, but does not alter regulatory T cell frequencies, which bear low levels of VDR [78].

The exact molecular mechanisms underlying the effect of vitamin D in MS is still elusive. However, the abundance of studies pointing at association of low vitamin D concentration and MS advocate for the beneficial role of vitamin D supplements as prophylactic and/or treatment agents. Clinical studies have indicated that large doses of 25(OH)D [79] and 1,25(OH)D [80] supplements are safe and well tolerated by MS patients. Even though disease progression and activity were not altered by 25(OH)D, the vitamin supplementation lead to reduction in gadolinium-enhancing lesions per patient as described by Kimball et al. [79]. The therapeutic effects of vitamin D supplements are currently being further investigated.

8.2. Smoking

A history of cigarette smoking has been almost unanimously associated with increased susceptibility to MS as asserted by a recent meta-analysis reviewing data on 14 studies including more than 3000 cases and 450 000 controls [81]. The authors, however, acknowledge that it is highly improbable that this environmental factor alone account for the worldwide variation in MS prevalence. A recent study by Hedstrom et al. suggested a significant interaction between smoking and two genetic risk factors of MS: presence of HLA-DRB1∗15 and absence of HLA-A∗02 [82]. Such interaction was not observed for non-smokers. Smoking increased the risk of MS in carriers of both genetic risk factors 2.8-fold, while only 1.4-fold increase was observed for individuals without the susceptibility alleles. The authors suggested that priming of T cell responses in the lung might contribute to the development of MS in genetically susceptible individuals.

It remains to be determined whether smoking is indeed an independent risk factor for MS development. The biological mechanisms that would link smoking to the pathogenesis MS are elusive. Nicotine, however, might not be the sole culprit since studies have shown that use of tobacco snuff does not increase the risk of MS [83,84].

9. Concluding remarks

Collaborative efforts during the past years achieved substantial progress in defining the genetic architecture, underlying susceptibility to MS. The role of environmental risk factors and their interaction with genetic susceptibility alleles are much less well defined, despite the fact that infections and non-infectious factors have long been associated with MS development. During the past decades, many reports that have claimed to identify environmental MS triggers, and almost universally these observations have later not withstood scrutiny. What we have learnt from these investigations is that association studies are inherently vulnerable to confounding factors such as selection bias and phenomena like reverse causality. Therefore, they require an adequate control for these confounding factors and reproducibility in independent cohorts. This applies to genetic studies but appears to be even more important for the analysis of environmental exposures.

Improvements in the design of epidemiological studies helped to identify consistent environmental risk-associations such as the increased susceptibility for MS in individuals with a history of IM, and the analysis of environmental effects will likely expand in the next few years. A future challenge lies in the design of studies that use this information to better understand the function of environmental susceptibility factors and their interaction with genetic risk variants for the development of MS. Insights gained from these studies could allow for the development of prevention strategies and more effective treatments for MS.

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