WILL ENVIRONMENTAL AND BEHAVIORAL CHANGES ALTER SUSCEPTIBILITY OR COURSE OF MS? – NO

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MS is a complex disease, the etiology of which includes both environmental and genetic determinants. The number of environmental and genetic determinants and their relative importance remain uncertain. No critical environmental and genetic determinant has been confidently demonstrated without which MS will not occur with the possible exception of Epstein Barr virus (EBV) seropositivity, which has been found to be almost universal in adults with MS. However, EBV seropositivity is found in the vast majority of individuals whether or not affected with MS. While there has been increasing optimism that at least two environmental factors, EBV exposure and vitamin D deficiency, may be finally be considered established as MS causal risk factors, the chances that these environmental factors will be confirmed or may be modified so as to influence susceptibility or course of MS is low. In support of this viewpoint, I will cite the following the arguments:

1. These environmental risk factors were not discovered through an unbiased search. Many other risk factors for MS have been proposed and refuted; others remain worthy of further study, including a variety of dietary factors, soil conditions as well as multiple viruses. The chances that EBV or vitamin D deficiency will have "staying power" after thorough investigation must be regarded as low based on historical success of identifying common etiological factors as causal for common diseases.
2. Many potential confounding associations limit an assessment of causality of these and other environmental factors, as outlined below.
3. The biological mechanisms underlying the effect of EBV or vitamin D on either the brain or immune function are unclear; many mechanisms have been proposed, most with little support. Without knowing the mechanism, it is hard to know what therapy to undertake, at what dose, and what intermediate outcomes/biomarkers might be helpful to evaluate.
4. Cofactors and their interactions with these risk factors are poorly understood, thereby complicating the identification of populations at particularly high risk and precluding the design of clinical studies with adequate power to address the question, even if the association is real and causal.
5. Required followup for any effective intervention would take decades to detect an effect.

I will discuss these arguments in relation to the two environmental risk factors for MS that have the greatest contemporary interest to MS investigators: EBV and vitamin D deficiency.

EBV is a virus that establishes lytic or latent infection of memory B cells. Several studies have documented high frequency of antibodies to a variety of EBV antigens, in particular EBNA1, years before MS begins. There is a higher frequency of clinical infectious mononucleosis in individuals with MS based on historical cohort studies. The difference in the rate of seropositivity in those with and without MS is particular evident in children. It appears that seronegativity for EBV is strongly, if not completely protective from development of MS. There also appears to be an interaction between EBV exposure and HLA DR15, the major susceptibility allele for MS. De Jager et al reported that the relative risk of MS among DR15-positive women with elevated (>1:320) anti-EBNA-1 titers was ninefold higher than that of DR15-negative women with low (<1:80) anti-EBNA-1 titers (PMID: 18362267). Yet, in spite of these findings, direct infection of the brain, although suggested by some, has not been confirmed. The pathogenetic mechanisms underlying the association of EBV with MS-related autoimmunity is unclear, although molecular mimicry has been proposed and there is some experimental evidence that would support antigenic similarities between myelin proteins and EBV; however, molecular mimicry arguments have been posited for a variety of viruses. Molecular events associated with MS pathogenesis

could also predispose to EBV infection or alter antibody responses, so that the apparent serological associations may not be causal, but may reflect co-association. Although the increased rates of EBV exposure antedate clinical symptoms of MS, it is difficult to be sure when MS begins. No vaccine exists for EBV, and EBV can exist in a latent state, complicating vaccine development. There are many potential complications of an altered but viable EBV vaccine, including lymphoproliferative disorders, which are potential complications of EBV. Furthermore, high titers of antibodies do not seem to protect against development of MS, but are indeed associated with MS. Unless they reflect ongoing infection, which is far from clear, it is unclear how boosting immune responses against EBV will be effective and doing so might even be deleterious.

Vitamin D is a vitamin with pleotropic functions, which likely include alteration of immune responses. Vitamin D receptors exist on a variety of immune cells. Vitamin D deficiency occurring decades before clinical onset has been associated with MS. It is a potential explanation for the geographic risk in terms of distance from the equator as vitamin D levels decrease as distance from equator decreases. Studies by my opponent have shown that vitamin D may regulate expression of HLA DR15 (NLM. PMC2627899), and a rare variant of CYP27B1, which affects the hydroxylase that converts 25-hydroxy to the active 1,25-dihydroxy form of vitamin D, may be associated with MS risk (UI: 22190362). Treatment with vitamin D has been reported to protect against experimental autoimmune encephalomyelitis. Treatment with vitamin D may favorably influence MRI activity in patients with established MS, although negative results have also been reported in small randomized clinical trials. However, despite these promising observations, vitamin D deficiency is ubiquitous, complicating analysis of its role in MS. The critical level of deficiency is difficult to define especially when the critical biological function underlying its putative effect in MS is unknown. A variety of confounders complicate the analysis of causality. For example, vitamin D deficiency is associated with lack of sun exposure and winter season, and winter is linked with increased frequency of respiratory infections, which have a strong association with MS relapse. MS patients might potentially have lesser exposure to the outdoors and sunlight. The geographic gradient of MS declining with distance from the equator might have a variety of explanations, including genetic differences in the population. In particular, the high proportion of northern Europeans living in areas with low UV radiation especially in winter months confounds analysis of whether vitamin D deficiency or European ancestry is the major explanation for the latitudinal gradient of MS. Although it is quite easy to treat or prophylax with vitamin D, identifying the critical at risk population (age, ethnicity, genetic background, basal vitamin D levels), controlling vitamin D use in controls, estimating the anticipated effect size, maintaining a study over adequate duration to determine the effect are all substantial hurdles that may limit a clear answer as to whether vitamin D replacement influences the rate of occurrence of MS.

Primary prevention of MS, though appealing, is a daunting task. It will require exclusion of confounding associations, establishment of biological effects and development of biomarkers, defining risk populations and estimating effect size, and probably very long follow-up before we will be able to conclude that modification of environmental risk factors or behaviors, including EBV and vitamin D intake, modifies the occurrence of MS.