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# Risk factors for multiple sclerosis: decreased vitamin D level and remote Epstein-Barr virus infection in the pre-clinical phase of multiple sclerosis

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A number of environmental and genetic factors are implicated in the complex aetiology of multiple sclerosis (MS). Among several types of environmental risk factors that have been considered, the major factors are thought to be low vitamin D concentration and Epstein-Barr virus (EBV) infection. Among vitamin D metabolites, 25-hydroxyvitamin D (25(OH)D) has been widely used to determine vitamin D status, and a large prospective study demonstrated an inverse correlation of 25(OH)D levels with the risk of MS among whites, which was particularly strong for 25(OH)D levels measured before 20 years of age.[1] EBV is a B-lymphotropic herpesvirus that establishes persistent latent infection in peripheral blood memory B cells. Epstein-Barr virus nuclear antigen-1 (EBNA1) is important for establishing and maintaining the altered state of cells following infection with EBV, and the risk for MS increases more than sevenfold with increasing titres of anti-EBNA-1 IgG antibodies.[2] Taken together, a low vitamin D level and EBV infection are plausible candidates for triggering and perpetuating MS. However, more data are needed from individuals who donated blood prior to the first clinical manifestation of MS to answer the question of whether long-term low vitamin D levels and indicators of remote EBV infection are associated with the risk factors for developing MS.

To help provide an answer, Décard *et al*[3] report on 25(OH)D levels and IgG response against EBNA1 during the preclinical phase in a German cohort. They found that serum 25(OH)D level was decreased in the 24 months before clinically isolated syndrome (CIS). They also report that IgG response against EBNA1 was increased in the 36 months before CIS. These findings suggest that the two major risk factors of low vitamin D level and remote EBV infection are important, especially during the few years prior to clinical manifestation. No direct relationship was observed between 25 (OH)D concentration and EBNA1 immunoreactivity in Décard *et al*'s study. Another study has reported that MS risk with increasing serum titres of anti-EBNA-1 IgG antibodies was not confounded by vitamin D.[2] Additional studies are needed to further our understanding of these risk factors in MS.

Further questions still remain. Geographical and racial/ethnic differences, in particular, seem to affect vitamin D levels. The aforementioned large prospective study that found a decreased risk of MS with increasing serum levels of 25 (OH)D among whites found no significant associations between vitamin D and MS risk among blacks and Hispanics.[1] Vitamin D levels are known to differ by race/ethnicity, so the question needs to be answered as to whether MS populations of different racial/ethnic background show the same tendency as the German cohort reported by Décard *et al*. Further, recent gene-environment interaction studies have demonstrated direct links between vitamin D and *HLA-DRB1*15*, the main susceptibility region in MS,[4] and that the positivity of *HLA-DRB1*15* differs by race/ethnicity. We might then need to consider environmental factors in correlation with genetic factors.

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## REFERENCES

1. **Munger KL,** Levin LI, Hollis BW, *et al*. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006;**296**:2832—8.
2. **Munger KL,** Levin LI, O'Reilly EJ, *et al*. Anti-Epstein-Barr virus antibodies as serological markers of multiple sclerosis: a prospective study among United States military personnel. *Mult Scler* 2011;**17**:1185—93.
3. **Décard B,** von Ahsen N, Grunwald T, *et al*. Low vitamin D and elevated immunoreactivity against Epstein-Barr virus before first clinical manifestation of multiple sclerosis. *J Neurol Neurosurg Psychiatry* Published Online First: 11 August 2012 doi:10.1136/jnnp-2012-303068.
4. **Handunnetthi L,** Ramagopalan SV, Ebers GC. Multiple sclerosis, vitamin D, and HLA-DRB1*15. *Neurology* 2010;**74**:1905—10.

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