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EXPOSURES ASSOCIATED WITH MULTIPLE SCLEROSIS DEVELOPMENT

Presymptomatic case-control studies

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Akademisk avhandling

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Avhandlingen kommer att försvaras på engelska.

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Abstract
Background: Multiple sclerosis (MS) is a chronic immune-mediated disease affecting the central nervous system. The current view is that MS is caused by a complex interplay of several environmental factors, eliciting an immune reaction in genetically susceptible individuals. Most previous studies of MS aetiology were retrospective, conferring the risk of reverse causation or recall bias. Few studies have been performed on data collected before the onset of the disease. The objective of this project was to identify risk factors for MS by analysing markers of exposure in samples collected before the clinical onset of MS.
Method: A series of nested case-control studies were performed by cross-linking Swedish MS registries with Swedish biobanks, thereby identifying serum or plasma samples from up to 837 cases who later developed MS. For each case, up to two matched controls were selected. The following environmental risk factors were assessed: Antibodies against herpesviruses Epstein-Barr virus (EBV), Human herpesvirus 6-A (HHV-6A) and Cytomegalovirus (CMV); Free Vitamin D_3 Index and Vitamin D Binding Protein (DBP); and C-reactive Protein (CRP). Early signs of neural injury were assessed by measuring the concentration of neurofilament light chain in serum (sNfL). The associations between the environmental factors and future development of MS were analysed with conditional logistic regression, calculating odds ratios (OR) with 95% confidence intervals (CI). Interactions were analysed on the multiplicative and additive scales. The temporal relation of HHV-6A serostatus and axonal injury was analysed with locally estimated scatterplot smoothing regression.
Results: Serological evidence of CMV infection was associated with a lower risk of MS development (OR = 0.70, 95% CI 0.56–0.88). Antagonistic interactions were observed between serological signs of CMV, HHV-6A, and EBV infection. Antibodies against HHV-6A were associated with a higher level of sNfL. In MS cases, increasing levels of HHV-6A antibodies were detected several years before increasing sNfL. Among young individuals, high levels of Free Vitamin D_3 Index were associated with a lower MS risk (OR = 0.37, 95% CI 0.15–0.91). In older individuals, high levels of DBP were associated with a lower risk of developing MS (OR = 0.36, 95% CI 0.15–0.85). Elevated levels of CRP were not associated with MS risk.
Conclusions: These results strengthen the evidence for HHV-6A and EBV in MS aetiology. They also support the hypothesis that CMV infection and a high level of free Vitamin D_3 during childhood and adolescence are associated with a lower risk of MS later in life.

Keywords
Multiple sclerosis, nested case-control studies, presymptomatic, Epstein-Barr virus, human herpesvirus 6A, cytomegalovirus, vitamin D

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