**MULTIPLE SCLEROSIS**

Immune response to EBNA1 predicts conversion to MS

Environmental factors such as viral infections are considered to be prominent risk factors for multiple sclerosis (MS). In a collaborative study, researchers from the MS Center of Catalonia, Vall d'Hebron University Hospital, Spain and The Institute of Experimental Immunology, Zurich, Switzerland found that elevated immune responses to Epstein–Barr virus (EBV) might predict conversion to MS in patients with clinically isolated syndrome (CIS)—a single neurological episode resulting from inflammation or demyelination that can develop into MS over time.

The pathophysiology of MS has been relatively well established, but the underlying etiology of the disease is poorly understood. The predominant hypothesis suggests that MS is caused by a viral infection, which initiates an inappropriate autoimmune response. Epidemiological studies have provided evidence that EBV could be an underlying cause of this disease. The prevalence of EBV infection is considerably higher among patients with MS than in the general population; in fact, virtually all individuals with MS are seropositive for EBV, and patients with CIS also show an increased propensity towards seropositivity for EBV. Previous work from the laboratory of Jan Lunemann,

University Hospital of Zurich, showed that T-cell and antibody responses to one particular EBV protein, the EBV nuclear antigen 1 (EBNA1), are prominently increased in patients with clinically definite MS.

In an attempt to discover whether viral infections are involved in the conversion of CIS to MS, Lunemann and colleagues investigated immune responses to several viruses that are prevalent in the human population, including human herpesvirus 6, cytomegalovirus, measles and EBV, in a cohort of 147 patients with CIS. By taking blood samples from the CIS cohort and analyzing the humoral and cellular immune responses to the various viruses, the researchers discovered that the immune response to EBNA1 was selectively increased in the patients with CIS. By contrast, immune responses to the other viruses were not increased in the CIS cohort when compared with controls. Furthermore, "[increased] humoral immune responses to EBNA1 were associated with...the number of T2 lesions [at baseline] and number of new T2 lesions at 1 and 5 years of follow-up, and with disability progression during follow-up," comments Manuel Comabella, of Vall d'Hebron University Hospital. Perhaps most importantly, however, the researchers showed that an
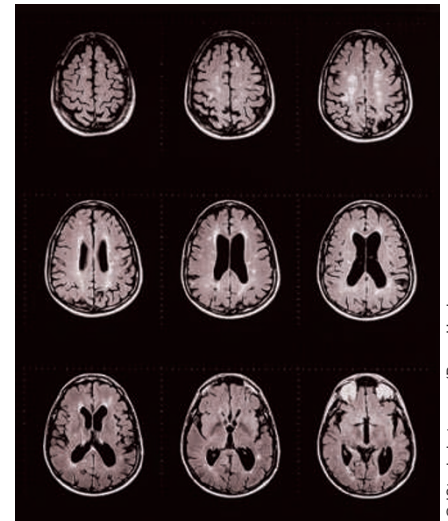
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increased immune response to EBNA1 was associated with a significantly heightened risk of conversion to MS.

"[The results] strongly suggest that EBNA1-IgG titers might be used as a prognostic marker for conversion to MS and disability progression," says Comabella. This finding could be important for the future development of prophylactic treatments for MS. Comabella concludes, however, that "our results do not necessarily imply a pathogenic role of EBNA1-specific immune responses in MS."

Nick Jones