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Commentary

Serum markers of multiple sclerosis - a new approach

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Optic neuritis (ON) typically manifests with the classical triad of subacute unilateral vision loss, periocular pain and impaired colour vision. It is the first symptom of multiple sclerosis (MS) in about 20% of patients, and approximately half of those experiencing ON will develop MS. However, other inflammatory diseases like neuromyelitis optica spectrum disease (NMOSD), systemic lupus erythematosus (SLE), sarcoidosis, Behchet's disease or infectious diseases like toxoplasmosis can also manifest with ON [1]. Thus, it is of crucial importance to improve the diagnosis of early MS. A number of paraclinical measurements can assist in providing a correct diagnosis, most notably magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examination [1]. Specific biomarkers for the differential diagnosis NMOSD have been developed, and most patients are tested for the specific antibodies AQP4-IgG and MOG-IgG on serum cell-based essays. However, no specific serological MS-biomarkers exist.

In the present paper recently published in *EBioMedicine*, Sadam and colleagues [2] take a new approach to the question of how to increase diagnostic accuracy in ON patients. By using mimotope variation analysis (MVA), a next generation phage display method, they detected two viral antibody epitopes as possible new biomarkers of MS-risk after ON. The epitopes were gB CMV and VCA p18 EBV. Their approach is interesting for several reasons: First, the biomarkers detected seem to improve the diagnostic accuracy for diagnosing MS in early ON. Second, they could point to pathogenic mechanisms for MS-development. Third, serum biomarkers are available from blood and are much easier to acquire than MRI and lumbar puncture.

Interestingly, although the authors have used a hypothesis-free approach, their findings point to two common viral pathogens, that have been linked to MS risk in epidemiological studies. While higher titres against Epstein-Barr virus (EBV) epitopes have been consistently found to increase the risk of developing MS [3], Cytomegalovirus (CMV) seropositivity has been negatively associated with MS risk [4]. The results of the current paper are in line with these previous findings. Sadam and colleagues [2] identified a clear negative association between epitopes against gB CMV and the risk of developing MS after ON. A negative association between previous infections with CMV and the risk of MS has been reported in one large Swedish population-based incident case-control study and in one small multi-ethnic US paediatric MS case-control study [5]. A more recent study found, however, inconsistency across ethnic groups [6], indicating that there might not be a causal association between CMV and MS.

More consistent epidemiological results have been found for the second potential biomarker, VCA p18 EBV [3,6], and some authors have suggested that MS could be considered a rare complication of EBV infection[7]. In one large study of early MS, it was found that 100% of the 901 patients were EBV positive, while controls did not reach 100% seropositvity in any of the investigated age cohorts [8]. Based on these findings, the authors suggested that negative EBV serology should alert clinicians to consider diagnoses other than MS. Most studies have examined the serum levels of EBNA-1, as a marker of previous EBV infection. In the present paper, the epitope VCA p18 EBV was found to be associated with risk of MS [2]. Interestingly, this could be consistent with the results from the Finish Maternity Cohort [7]. In this study, offspring of mothers with high VCA IgG during pregnancy had an increased risk of developing MS. The mechanism for how this could affect MS risk is however, still not determined.

A number of precautions have to be taken before these biomarkers can be used in a clinical setting. First, the results should be replicated in larger independent cohorts. Preferentially, prospective cohort studies could examine the benefit of incorporating these biomarkers in a risk-evaluation scheme. Second, the biomarkers must be evaluated in different ethnic populations to determine if the findings are consistent across ethnic and regional groups. Based on previous trials, especially CMV antibody responses seem to be determined by ethnicity and possibly not causally linked to the risk of MS. Third, the sensitivity and specificity was only at 75%. We know that about half of all ON patients will go on to develop MS, and the diagnostic accuracy is still far from perfect. These potential biomarkers will probably need to be supplemented with other markers to improve their diagnostic accuracy.

In summary, the present study adds to the growing number of findings, indicating that the immunological response to the herpes viruses CMV and EBV are linked to the risk of developing MS. This could reflect unique pathogenic mechanisms for how MS develops and could possibly improve future treatment and diagnosis of the disease.

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Declaration of Competing Interest

The author reports no conflicts of interest.

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