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Epstein-Barr virus DNA in the cerebrospinal fluid of multiple sclerosis patients and controls.

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Introduction:

Epstein-Barr virus (EBV) is an outstanding risk factor for multiple sclerosis (MS). However, there are contradictory findings on the presence of the virus in the central nervous system (CNS) in MS. We examined the presence of EBV DNA in the cerebrospinal fluid (CSF) and blood in MS patients and controls using a highly sensitive droplet digital PCR (ddPCR) and applied a probabilistic method to estimate the number of EBV positive B-cells in blood and CSF.

Objectives/Aims:

To determine, if EBV is detectable in the CSF, to estimate the number of EBV positive cells in the CSF and blood and to analyse viral activation in peripheral blood lymphocytes in MS patients and controls.

Methods:

CSF samples were collected at diagnostic lumbar punctures from 45 MS patients and 45 controls with other conditions, matched by the carriership of HLA-DR15. CSF supernatants and cells were separated, live cells were aliquoted and cellular DNA amplified with Phi polymerase. Representative sample of CSF cell-derived DNA was obtained in 28 cases and 28 controls. In a subset of samples, non-amplified DNA from CSF cells and blood B-cells was analysed. For EBV DNA detection we used ddPCR. Multiple ddPCRs were performed in each sample. We estimated the number of B-cells in each reaction and based on the observed DNA detection rates calculated the expected frequencies of EBV positive B-cells in the CSF and blood. To detect viral RNA as a sign of activation, RNA sequencing was performed in separated blood CD4, CD8 and CD19 positive cells from 21 MS patients and 3 controls.

Results:

All subjects were EBV seropositive. One (3.6%) of the MS patients, none of the controls, was positive for EBV DNA in cell-free CSF. Cellular DNA of the CSF was analysed in six independent ddPCRs: EBV-DNA was detected in 12 (43%) of the 28 MS patients and 13 (46%) of the 28 controls in at least one of the tests. The difference between the groups was not statistically significant. The probabilistic analyses suggest that all EBV seropositive subjects have EBV DNA in the CSF B-cells, if enough B-cells would be available for the analysis. In the subjects studied here, the number of EBV positive B-cells appears higher in the CSF than in the blood. We did not detect viral RNA in the blood CD4, CD8 and CD19 positive cells.

Conclusion:

EBV-DNA is detectable in the CSF cells of both MS patients and controls with ddPCR, and the probabilistic approach indicates that the true positivity rate approaches 100% in EBV-positive individuals. There doesn't seem to exist a mechanism prohibiting access of EBV-positive B-cells to enter the CNS.

Disclosures:

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