Background
Progressive multifocal leukoencephalopathy (PML), caused by JC virus (JCV), remains a devastating brain opportunistic infection in HIV-infected individuals but has also become a complication of treatment with novel immunomodulatory agents. Natalizumab, a monoclonal antibody against integrin alpha-4, provides effective treatment for multiple sclerosis (MS) by preventing leukocytes from entering the brain. However, as of January 2014, 428 PML cases have been reported in natalizumab-treated MS patients. The pathogenesis of JCV reactivation remains elusive.

Objectives
1. Characterize JCV detection in CSF, PBMC subpopulations, plasma and urine among natalizumab-treated MS patients.

Methods
N=43 JCV seropositive MS patients, cross-sectional study
- Blood: Ficoll, PBMC cytometry sorting: CD34+ cells, B cells, Monocytes, T cells, NK cells
- Urine

Results
JCV DNA was detected in the CSF of 2/34 (5.9%) subjects tested with no symptoms of MRI lesions consistent with PML and in PBMC of 12/43 (27.9%) subjects but not in plasma. Detection within different PBMC subpopulations is shown above. Viruria was detected in 11/43 (25.6%) subjects.

Conclusions
1. Asymptomatic JCV reactivation may occur in the CSF of natalizumab-treated MS patients after 18 months of therapy. Therefore, in the absence of new clinical or MRI findings, JCV detection in CSF is not equivalent to PML.
2. JCV is associated with multiple circulating mononuclear cell subpopulations and viral load is higher in CD34+ cells and monocytes compared to other cell types.
3. Viremia might trigger a JCV-specific CD4+ -mediated response that can be detected by ICS.
4. JCV DNA detection in PBMC, but not in plasma or urine, may be a surrogate marker for viral reactivation.
5. In vitro stimulation with JCV peptides allows enhanced detection of JCV-specific cellular response, which is highly prevalent in all MS patients, regardless of treatment, and is mediated by CD4+ and CD8+ T cells.

JCV DNA load was higher in CD34+ cells compared to B (p=0.006), T (p=0.004) and polymorphonuclear (PMN) (p=0.002) and in monocytes compared to T cells (p=0.005) and PMN (p=0.004)

JCV-specific T cell detection by ELISpot and ICS

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