Intrathecal B-cell inflammation may mediate cortical pathology in multiple sclerosis at time of diagnosis by influencing macrophage and haemoglobin activity.

*S. Rossi[1, 2], S. Hametner[3], F. Lattanzi[1], D. Marastoni[1], M. Castellaro[1], G. Farina[1], V. Mazziotti[1], C. Senatore[2], A. Gajofatto[1], MD. Benedetti[1], S.Monaco[1], F. Facchiano[2], M. Calabrese[1], R. Magliozzi[1, 4.]

*Main author

[1]Neurology B, Dept. of Neurological and Movement Sciences, University of Verona, Italy

[2]Istituto Superiore di Sanità, Oncology and Molecular Medicine, Rome, Italy

[3]Neuroimmunology Department, Centre for Brain Research, Medical University of Vienna

[4]Division of Brain Sciences, Department of Medicine, Imperial College London, United Kingdom,

Objectives: Meningeal inflammation in cerebral sulci of MS patients was suggested associated with increased neuronal/microglia alterations in the adjacent grey matter (GM) according to a gradient "surface-in" (1) from pial surface towards white matter. Up to now, possible mechanisms mediating differential cortical microglia/macrophage activation and pathology remain still unknown.

Methods: CSF from 64 MS patients and 25 controls has been collected at time of diagnosis. For each patient clinical assessment and 3D DIR 3T-MRI imaging to characterize cortical lesions was performed and combined with detailed proteomic and protein analysis of 69 inflammatory mediators (Bio-Plex).

Results: The presence of high CSF levels of B-cell related mediators (CXCL13,CXCL12,CXCL10,BAFF,IL6,IL10,GM-CSF,TNF) was found strongly linked to increased number and volume of cortical lesion of a subgroup (56,25%) of the examined MS patients. Concomitant significant high protein levels of sCD163, marker of activated macrophages, were found in the CSF of the same MS group and positively ($p<0.001$) correlated with levels of BAFF ($r=0.4$), IL10 ($r=0.5$), CXCL13 ($r=0.5$), CXCL12 ($r=0.5$) and TNF ($r=0.5$). Furthermore, sCD163 CSF protein levels significantly correlated with levels of free-haemoglobin ($r=0.4$; $p= 0.04$) and neurofilament-light ($r=0.532$; $p<0.001$) in the CSF of the same MS patients. On the contrary, increased levels of sCD14 was detected in the CSF of MS patients with lower GM lesion load and significantly correlated with high protein levels of IFN-λ2 ($r=0.5$, $p= 0.0006$).

Conclusions: CSF B-cell activity may play key roles in MS cortical damage at the diagnosis by influencing different intracerebral macrophage activity, reflected by high CSF levels of sCD163 and

free-hemoglobin. By contrast, association between sCD14, IFN-λ2 and mild degree of cortical pathology, suggests protecting role of innate immunity, deserving further analysis. Combined CSF and MRI profiling at the diagnosis represent a potential tool to predict/monitor intrathecal inflammation and cortical pathology.

References:

1_ Magliozzi et al., Annals of Neurology 2010