PERMEABILITY OF THE BLOOD-BRAIN BARRIER PREDICTS CONVERSION FROM OPTIC NEURITIS TO CLINICALLY DEFINITE MULTIPLE SCLEROSIS

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Purpose: To investigate whether blood-brain barrier (BBB) permeability is increased in normal appearing brain tissue of patients diagnosed with Optic Neuritis (ON) compared to that of healthy controls. In 50% of ON cases, the patient will later develop Multiple Sclerosis, hence we aimed to investigate if BBB permeability could predict later conversion to Clinically Definite Multiple Sclerosis[1]. Furthermore, we wanted to investigate if BBB permeability is correlated with inflammatory markers from the cerebrospinal-fluid (CSF); leukocyte count, IgG-index and biomarkers for inflammation and cellular trafficking, namely matrix-metallo-protease-9 (MMP-9), C-X-C chemokine ligand 10 (CXCL-10) and CXCL-13. **Methods:** Dynamic contrast-enhanced MRI at 3T[2] was used to measure BBB permeability in 31 ON patients, all referred for MRI as part of diagnostic workup at time of diagnosis. Measurements were compared with 17 healthy controls matched for age and gender. Patients had MRI and lumbar puncture performed within 2 weeks of onset of ON symptoms. **Results:** We found a significantly higher (p=0.006) permeability of the BBB in periventricular normal appearing white matter (NAWM) in the total cohort of ON patients compared to healthy controls. In normal appearing grey matter and thalamic tissue, no such difference was found. Pooling ON patients and healthy controls we found that BBB permeability correlated with the following CSF markers: Leukocyte count (PCC (Pearson Correlation Coefficient) 0.56; p=0.0002), IgG index (PCC 0.33; p=0.04) and biomarkers CXCL10 (PCC 0.38 p=0.15), CXCL13 (PCC 0.38, p=0.017) and MMP9 (PCC 0.42, p=0.007). In ON patients with conversion to CDMS within 1 year after initial diagnosis of ON we found significantly higher BBB permeability in periventricular NAWM (2 tailed T test; p=0.01), see figure 1. **Discussion:** The finding of higher BBB permeability in periventricular NAWM in the subgroup of ON patients who developed MS within the first year after ON onset, emphasize the importance of BBB pathology in NAWM, an area prone to development of new MS lesions. However, we also find a significantly higher permeability in ON patients who did not convert to MS, when compared to healthy controls, a finding which could indicate that BBB permeability is linked to non-specific CNS inflammation. However, an important limitation to this observation is the presumably low conversion rate from monosymptomatic ON to MS within one year. We find a significant correlation between BBB permeability in NAWM and several CSF markers of inflammation and cellular trafficking, which seems to confirm the validity of BBB permeability as a marker of CNS inflammation. A breach in the BBB seems to result in a spill over from the blood into the CSF, of cells, antibodies and signaling molecules. We have previously found abnormal BBB permeability in NAWM of untreated MS patients compared to healthy controls (submitted), and interestingly the absolute level of permeability is about the same in the ON patients with later conversion to CDMS (K^{trans} 0.09 and 0.06 mL/100g/min, respectively), arguing that widespread BBB pathology could be central in the pathophysiology of MS. **Conclusions:** Our results emphasize the importance of BBB pathology in both ON and MS, and confirm the validity of measuring BBB permeability as a marker of CNS inflammation. Measuring BBB permeability could be an important supplementary prognostic marker for determining later conversion from Optic Neuritis to MS.

Figure 1: BBB permeability and conversion from ON to CDMS within 1 year

References: 1. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol.* 1983 Mar;13(3):227–231. 2. Larsson HBW, Courivaud F, Rostrup E, Hansen AE. Measurement of brain perfusion, blood volume, and blood-brain barrier permeability, using dynamic contrast-enhanced T1-weighted MRI at 3 tesla. *Magn Reson Med.* 2009 Nov;62(5):1270–1281.