An imaging signature in choroid plexuses in pre-symptomatic multiple sclerosis

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Introduction

The choroid plexuses (CPs) are a blood-cerebrospinal fluid interface with key immunosurveillance functions.[1] Their structural and functional alterations might contribute to the pathophysiology of immune-mediated central nervous system (CNS) diseases like multiple sclerosis (MS). We have recently provided, using magnetic resonance imaging (MRI) and translocator protein (TSPO) inflammatory positron emission tomography (PET), an *in-vivo* evidence of CP involvement in MS.[2] Studies on animal models of MS have shown that these structures play an early role in disease onset, being responsible for the initial lymphocytic infiltration of the CNS.[3] In human pathology, this early, pre-symptomatic phase of the disease can be sometimes identified as radiologically isolated syndrome (RIS). Therefore, we investigated whether CP changes found in defined MS are already detectable *in vivo* at the RIS stage.

Subjects and Methods

27 pre-symptomatic MS subjects, 97 clinically definite MS (CDMS) patients and 53 healthy controls (HC) underwent 3T-MRI; of which, 37 MS, 19 HC and one pre-symptomatic MS underwent TSPO ^{18}F-DPA-714 PET. T2-hyperintense lesions were contoured using Jim, while CPs were manually segmented on 3DT1-weighted images for volumetric analysis. Whole brain and lateral ventricle volume were extracted with Freesurfer. CP ^{18}F-DPA-714 uptake, reflecting inflammation, was calculated as the average standardized uptake value ($SUV_{60\text{-}90}$, **Fig. 1**). Oligoclonal band (OCB) status, duration of follow-up and conversion to CDMS were collected for the pre-symptomatic cohort.

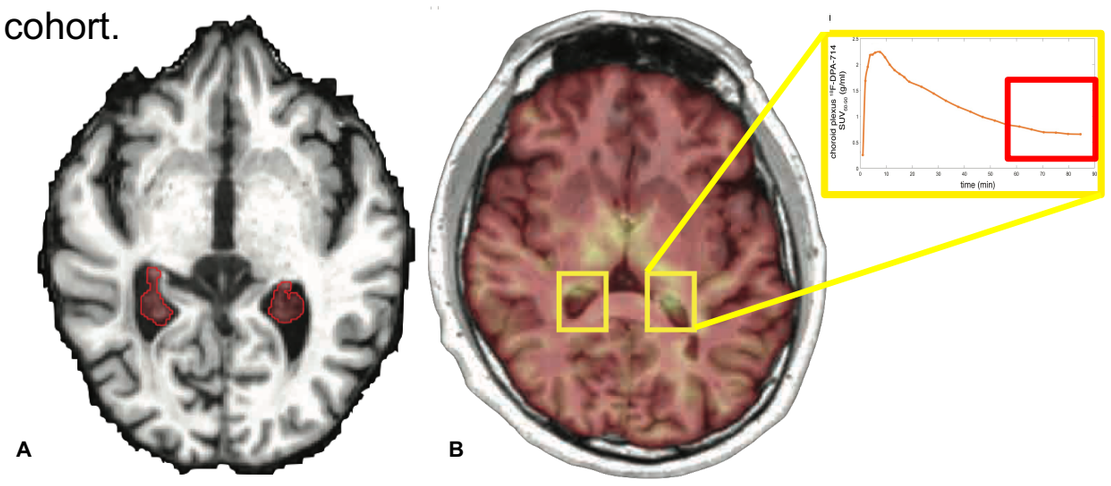

Figure 1. CP segmentation on the 3DT1 image (**A**) and SUV extraction (**B**) from 60 to 90 min.

Additionally, post-mortem CP samples from MS and HC were analyzed to study TSPO co-expression with immune cell markers (CD3, CD20, CD68, CD163). Group differences in CP volume were tested using multivariable regressions adjusted for age, sex, ventricular and brain volume. For the pre-symptomatic case who also had ^{18}F-DPA-714-PET, CP $SUV_{60\text{-}90}$ differences with MS and HC were assessed through Crawford-Howell test.

Results

CP volume was 29% higher in pre-symptomatic MS subjects compared with HC, even when accounting for brain and ventricular volume (RIS volume:14.9±5.2x10^{-4}, HC volume:11.3±3.9x10^{-4}, ß=0.31,p=.009, **Fig. 2**), and was not different from CDMS (volume:15.9±4.5x10^{-4}, p=.21). Within the pre-symptomatic group, CP volume did not differ on the basis of the OCB or the converter status (p=.66 and p=.85, respectively).

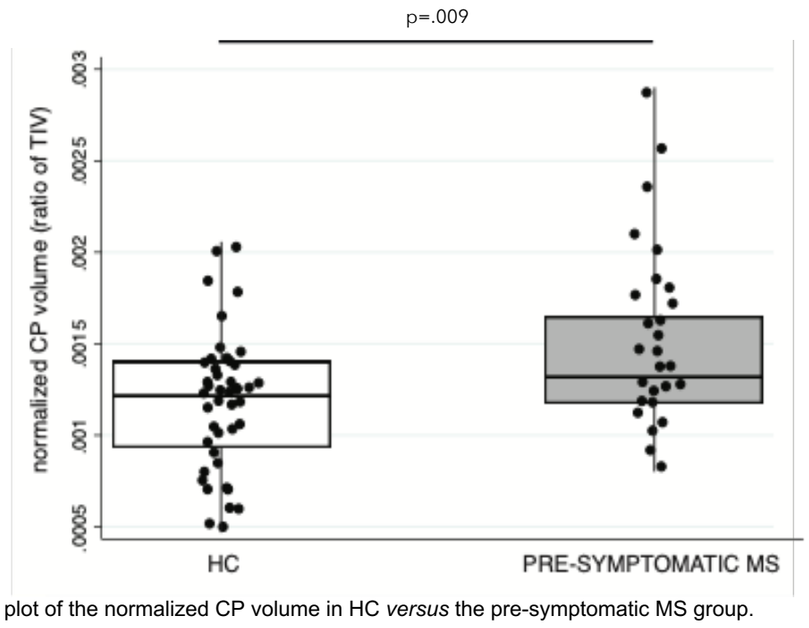

Figure 2. Box plot of the normalized CP volume in HC *versus* the pre-symptomatic MS group.

In the single pre-symptomatic case, CP ^{18}F-DPA-714 binding, reflecting TSPO expression, was 33% higher than in HC (**Fig. 3A**, $SUV_{60\text{-}90}$ case:0.794, HC:0.596±0.13, p=.04), but was not different from CDMS ($SUV_{60\text{-}90}$:0.887±0.22, p=.17). CP histology showed epithelial TSPO (brown) expression in both MS and HC, with an additional stromal infiltration of TSPO+ cells positive for the monocyte/macrophage marker CD163 (red)(**Fig. 3B-C**) only in patients, which could explain the higher uptake found in MS.

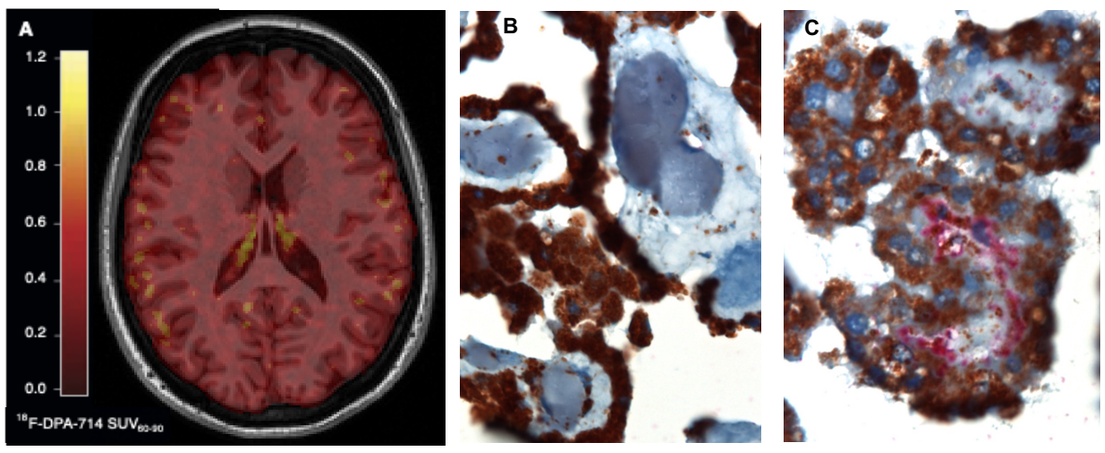

Figure 3. $SUV_{60\text{-}90}$ map of the case (**A**); post mortem CP sections from a HC (**B**) and an MS (**C**) showing infiltration of TSPO+/CD163+ macrophages in the CP stroma of MS.

Discussion and Conclusion

CPs are already enlarged at the pre-symptomatic MS stage compared with HC. They also have a TSPO overexpression as seen with ^{18}F-DPA-714-PET, likely due to CD163+/TSPO+ macrophages with antigen-presenting functions in MS.[4] Our findings identify an imaging signature in CPs before symptom onset, encouraging further investigation on its potential role as biomarker and arguing for the early involvement of the blood-cerebrospinal fluid barrier dysfunction in disease development.

[1] Ghersi-Egea et al, 2018; [2] Ricigliano et al, 2021; [3] Reboldi et al, 2009; [4] Ivan et al, 2021.