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

SHORT TITLE: Imaging signature of choroid plexus in RIS

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Objective: To assess choroid plexus (CP) alterations in pre-symptomatic multiple sclerosis (MS).

Background:*In vivo* evidence of CP involvement in MS has been recently shown, but whether CP changes are detectable by imaging before symptom onset, at the stage sometimes identified as radiologically isolated syndrome, needs to be investigated.

Design/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 translocator protein ^{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). Oligoclonal band (OCB) status, duration of follow-up and conversion to CDMS were collected for the pre-symptomatic cohort. Multivariable regressions adjusted for age, sex, ventricular and brain volume were fitted to test CP volume differences: i) between pre-symptomatic subjects and MS or HC; ii) within the pre-symptomatic group, between OCB-positive *versus* OCB-negative subjects, and converters *versus* non-converters (additionally accounting for the length of follow-up). For the single pre-symptomatic case who also had ^{18}F-

DPA-714-PET, CP SUV 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 (ß=0.31,p=.009), and was not different from MS (p=.21). Within the pre-symptomatic group, CP volume did not differ on the basis of the OCB or the converter status. In the single pre-symptomatic case, CP ^{18}F-DPA-714 binding was 33% higher than HC's (p=.045).

Conclusions: Our findings identify an imaging signature in CPs before symptom onset, encouraging investigations on its role as biomarker and arguing for the early involvement of the blood-cerebrospinal fluid barrier of the CPs in MS pathophysiology.

Declaration: All Authors are aware of and agree to the content of the abstract and support the data presented.

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