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Choroid plexus volume differentiates MS from its mimics

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Abstract

This study aimed to determine whether choroid plexus volume (CPV) could differentiate multiple sclerosis (MS) from its mimics. A secondary analysis of two previously enrolled studies, 50 participants with MS and 64 with alternative diagnoses were included. CPV was automatically segmented from 3T MRI, followed by manual review to remove misclassified tissue. Mean normalized CPV (nCPV) to intracranial volume demonstrated relatively high specificity for MS participants in each cohort (0.80 and 0.76) with an area under the receiver-operator characteristic curve of 0.71 (95% CI=0.55–0.87) and 0.65 (95% CI=0.52–0.77). In this preliminary study, nCPV differentiated MS from its mimics.

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Keywords

multiple sclerosis; diagnosis; differential diagnosis; misdiagnosis; biomarker; MRI

Introduction:

Recent literature has highlighted the potential role of the choroid plexus (CP) in neuroinflammatory processes in MS and demonstrated associations between CP volume (CPV) and key MRI and clinical outcomes. CPV enlargement has been demonstrated in early MS[1] and CPV has been associated with MRI gadolinium enhancing lesions, larger white matter lesion burden, expansion of chronic lesions, deep grey matter atrophy, cortical atrophy, higher annualized relapse rate, increased disability status scale scores, and more disability progression.[2–4] Although data are limited, CP enlargement was not found in two disorders known to frequently mimic MS – migraine and neuromyelitis optica spectrum disorder (NMOSD).[2] Thus, choroid plexus volume (CPV) could also be a candidate diagnostic imaging biomarker for MS. Through implementation of a novel automated segmentation method in two different cohorts with varied MRI protocols and scanners, this study aimed to evaluate an association between choroid volume and MS diagnosis.

Methods:

This secondary analysis of previous CAVS-MS[5] and University of Vermont (UVM)[6] MS diagnostic biomarker studies included 50 participants who fulfilled 2017 diagnostic criteria for MS (48 RRMS and 2 PPMS) and 64 participants who did not fulfill diagnostic criteria (Supplementary Tables 1, 2). The CAVS cohort was comprised of new MS evaluations whereas the UVM cohort was comprised of patients with longstanding diagnoses. Due to these differences and to demonstrate generalizability, the cohorts were analyzed both separately and in combination. The study was approved by the UVM Institutional Review Board (IRB) and at all CAVS-MS participating site IRBs. Written informed consent was obtained from all participants.

3T MRIs were performed on four different systems[5, 6] including T1-weighted sequence (isotropic resolution 0.8 mm for UVM and 1.0mm for CAVS-MS) with 3D sagittal acquisition of the entire brain. CP was automatically fully segmented and total intracranial volume (ICV) measured on 3D T1-weighted MPRAGE sequences using FreeSurfer 7.1.1, and an error correction method based on CP morphometry and symmetry was applied (Image Processing in supplemental material). Automatic segmentation was manually reviewed by a board-certified neurologist (EL). The CPV was normalized to ICV accounting for variations in brain size (nCPV = CPV / ICV, unitless). ComBat,[7] a statistical approach which mitigates inter-scanner biases, was applied to harmonize derived volume-related data, with the MS diagnosis variable protected (Supplementary Figures 1, 2).

A two-sample *t*-test with Welch's correction for unequal variances was conducted to compare average nCPV between MS and non-MS. Logistic regression of MS diagnosis was conducted in terms of nCPV, sex, and age as differences have been described in normal CP physiology.[8, 9] Receiver-operator characteristic curve (ROC) analysis was employed to

assess the diagnostic performance of nCPV using the area under the curve (AUC). Youden's J statistic was used to determine the threshold of nCPV that optimizes both sensitivity and specificity.

Results:

Baseline participant characteristics have been published previously[5, 6] (Supplementary Table 3). MS participants in CAVS-MS had a shorter duration between clinical onset of MS and study enrollment than UVM participants ($p< 0.001$). Non-MS participants in the CAVS-MS cohort were older ($p=0.003$) and more likely to be female ($p=0.007$) compared to the MS participants. There were no significant differences regarding age and sex in the UVM Cohort between the MS and non-MS.

Table 1 demonstrates that the mean nCPV of MS participants was greater than non-MS participants in each cohort (24% and 13%). According to the logistic regression model (Table 1), nCPV differed with MS diagnosis across both cohorts. On average, for every standard deviation increase of nCPV, the odds of MS increased by 2.86 times (odds ratio, 95% CI=1.29–8.07, $p=0.023$) in the UVM Cohort and 1.64 times (95% CI=1.02–2.74, $p=0.048$) in the CAVS-MS Cohort. The odds ratio estimates yielded similar conclusions while the confidence limits shifted when accounting for demographics (sex and age) in both cohorts. nCPV demonstrated relatively high specificity in each cohort (0.80 and 0.76) and low sensitivity (0.55 and 0.50). As shown in Figure 1, the overall AUC was 0.71 (95% CI=0.55–0.87) in the UVM cohort and 0.65 (95% CI=0.52–0.77) in the CAVS-MS cohort.

Discussion:

In this study, MRI evaluation of CPV differentiated MS from its mimics with relatively high specificity utilizing clinically routine sequences and widely available segmentation techniques. Previous data are limited to two studies that found increased CPV in MS patients compared to patients with NMOSD and migraine.[4, 10] Importantly, from the perspective of a potential diagnostic biomarker, CP enlargement appears to begin early in disease course of MS.[2] Persistent barriers to early MS diagnosis and increased risk of confounding comorbidities with age also necessitate its evaluation in older populations. Inclusion of both the CAVS-MS and UVM cohorts in this study demonstrates preliminary data supportive of CPV as a diagnostic aid in both new evaluation for suspected MS and across a range of disease durations. Particularly as automated approaches incorporating putative MRI diagnostic biomarkers are validated in MS, integration of CPV as an adjunctive measure to other neuroimaging findings amenable to automated assessment and with specificity for MS pathology may further improve diagnostic accuracy.

There were limitations to this study. The UVM Cohort was a cross-sectional convenience sample that was predominantly female, while CAVS-MS was more sex-balanced. The time from clinical onset of MS to study enrollment was longer in the UVM cohort than CAVS, without difference in nCPV (Supplementary Figure 5). In the CAVS cohort the average disease duration was 4 years, and therefore the performance of nCPV as a tool to aid diagnosis in very early MS requires further data. CPV is presumed to be associated

with neuroinflammation, and disease modifying therapy (DMT) might attenuate CPV changes.[11] However, most (17/20) of the UVM MS participants were receiving DMT at the time of study participation.[6] Given that others have found enlarged CP in presumably noninflammatory neurodegenerative diseases,[12] further data is needed to understand the causes of CPV changes in neurological disease. In subjects who were ultimately not found to have MS, there was a wide range of final diagnoses (Supplementary Table 2). Larger future studies in patients undergoing evaluation for MS will be needed to include the breadth of disorders that may be mistaken for MS, evaluate variability of CPV segmentation and whether contrast enhanced T1 imaging improves segmentation, and to assess the effects of MS DMT on CPV. Despite these limitations, our preliminary data justify further study of CPV as a MS diagnostic biomarker.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

Data is available upon reasonable request.

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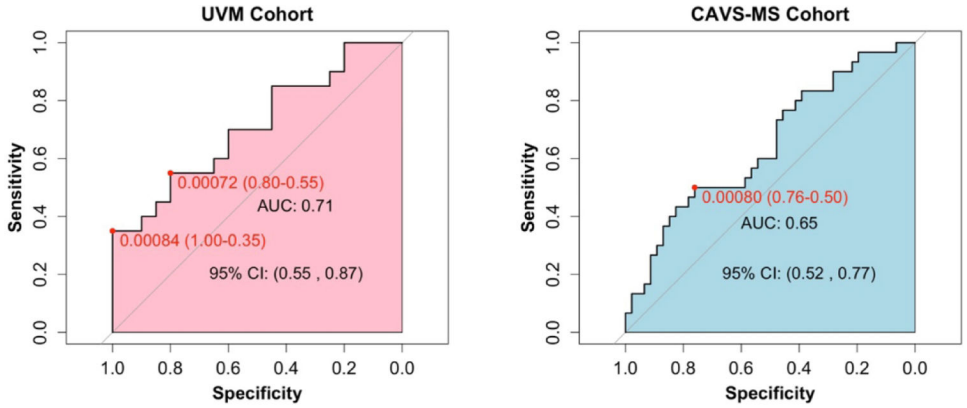

Figure 1.

Receiver operating characteristic (ROC) curve demonstrating sensitivity and specificity of choroid plexus volume for MS. Optimal nCPV threshold is given in red as threshold (specificity-sensitivity). The UVM Cohort has two optimal nCPV thresholds that both maximize Youden's J statistics due to a relatively small sample size. The nCPV threshold of 7.2×10^{-4} was chosen as it provided a better balance between specificity and sensitivity.

Table 1.

Mean choroid plexus volume and logistic regression results.

Mean choroid plexus volume				
Cohort	**MS**	**Non-MS**	**P-value**	**Volume Type**
UVM	7.8×10^{-4} (2.2×10^{-4})	6.3×10^{-4} (1.4×10^{-4})	0.011	nCPV
CAVS-MS	7.8×10^{-4} (2.0×10^{-4})	6.9×10^{-4} (1.8×10^{-4})	0.050	nCPV
UVM	1123.30(351.55)	891.52(217.76)	0.018	CPV
CAVS-MS	1170.73(323.67)	1104.19(270.32)	0.024	CPV
Logistic Regression				
Cohort	**Estimates**	**Odds**	**95% CI**	**P-value**
UVM	1.05	2.86	1.29–8.07	0.023
CAVS-MS	0.50	1.64	1.02–2.74	0.048
Logistic Regression (Sensitivity Analysis)				
UVM	1.44	4.23	1.59–16.00	0.012
CAVS-MS	0.55	1.74	0.99–3.19	0.060

nCPV: normalized choroid plexus volume to intracranial volume (unitless); CPV: choroid plexus volume (mm^3); Values for nCPV and CPV are given as mean (standard deviation); P-value: statistical significance of the difference in mean nCPV, CPV between MS and Non-MS groups (for mean choroid plexus volume), and statistical significance of nCPV's effect on MS diagnosis (for logistic regression); 95% CI: 95% confidence interval of the odds; Odds: the ratio of MS to Non-MS; Logistic Regression: logistic regression on standardized nCPV; Logistic Regression (Sensitivity Analysis): logistic regression further adjusting for age and sex.