Ventricular Volume as the Most Informative Biomarker of TSPO-PET Binding Status in Multiple Sclerosis Patients

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INTRODUCTION

Ability to identify multiple sclerosis (MS) patients burdened by smouldering inflammation is of great importance for therapeutic and clinical trial purposes [1]. PET imaging using 18 kDa translocator protein (TSPO)-binding radioligands can be used as an imaging biomarker for quantitation of glial activation in vivo [2]. However, large scale use of PET is challenging. Proxy biomarkers for TSPO-PET outcomes would therefore be helpful.

OBJECTIVES

The objective of the study was to identify key predictors of high TSPO-binding status in MS brain (HOT-PET phenotype) to provide widely usable tools for identification of patients with significant smouldering inflammation. Moreover, establishing a valid link between TSPO-PET and MRI measures would support the use of MRI as a proxy for microglial activation, given the limited accessibility of TSPO-PET.

METHODS

The sample included 128 MS patients (92 RRMS, 36 progressive). 3T magnetic resonance imaging (MRI) was performed and the images were processed in MATLAB and segmented using FreeSurfer. PET imaging using the TSPO-binding radioligand [11C]PK11195 was performed. Patients were classified according to their TSPO binding status: threshold for HOT-PET was set at 9.6% of active voxels in the white matter (based on TSPO-binding in an SPMS cohort). Partial least squares discriminant analysis (PLS-DA) extracted independent subspaces of variables best explaining outcome variability (high or low TSPO-PET binding status). Based on variable importance in projection (VIP) scores, significant predictors of high TSPO binding were combined into a decision tree model to quantify misclassification error and refine the predictive framework [3,4].

RESULTS

Based on the highest VIP scores, we constructed a decision tree using MRI-derived features alone. Ventricle parenchymal fraction (%PF) consistently emerged as a key predictor across all models, with a stable threshold around 2.12%. When combined with thalamus %PF, brain %PF, and age, and after tuning model parameters, we achieved an improved test accuracy of 0.84, outperforming the ventricle-only model (accuracy = 0.74). Key decision nodes included ventricle %PF ≥ 2.12 and age ≥ 38.4, which were strongly associated with the HOT-PET phenotype. Even among patients with smaller ventricles, low thalamic and brain %PFs contributed to identifying those with high glial activation.

To further characterize these patterns, we plan to stratify patients by MS subtype (RRMS vs PMS) and ventricle size, assessing whether enlarged ventricles in RRMS suggest a progressive-like inflammatory profile or whether some PMS patients with preserved brain volumes show lower microglial activation.

CONCLUSION

MRI-based volumetrics offer a practical strategy to identify MS patients with high glial activation when PET is unavailable or difficult to perform. While ventricle PF% alone was a strong proxy biomarker, classification improved by including

DOI: 10.54103/2282-0930/29290

thalamus and brain volume PF%, as well as age. This multivariable approach can support better patient stratification for phase 3 trials targeting microglial activation and help clinicians screen those most likely to benefit from microglia-targeted therapies.

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DOI: 10.54103/2282-0930/29290