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Widespread Glial Activation in Primary Progressive Multiple Sclerosis Revealed by ^{18}F-PBR06 PET

A Clinically Feasible, Individualized Approach

Tarun Singhal, MD,† Eero Rissanen, MD, PhD,* John Ficke, BA,* Steven Cicero, BS,* Kelsey Carter, MSN,* and Howard L. Weiner, MD†*

Abstract: A 64-year-old man with primary progressive multiple sclerosis (Expanded Disability Status Scale 3.5) underwent PET using ^{18}F-PBR06, a second-generation 18-kDa translocator protein ligand targeting activated brain microglia and astrocytes. Voxel-by-voxel statistical comparison of patient's PET images (acquired 60–90 minutes postinjection) with a healthy control data set was performed to generate a 3-dimensional *z*-score map of increased radiotracer uptake, which showed widespread increased glial activation in normal-appearing cerebral white matter, white matter lesional and perilesional areas, brainstem and cerebellum. In contrast, patient's 3-T MRI scan showed only a few small white matter brain lesions without contrast enhancement.

Key Words: astrocytes, PPMS, microglia, neuroinflammation, TSPO PET

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From the *PET Imaging Program in Neurologic Diseases and †Partners Multiple Sclerosis Center, Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

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Correspondence to: Tarun Singhal, MD, PET Imaging Program in Neurologic Diseases, Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Building for Transformative Medicine, 60 Fenwood Rd, Boston, MA 02115. E-mail: tsinghal@bwh.harvard.edu.

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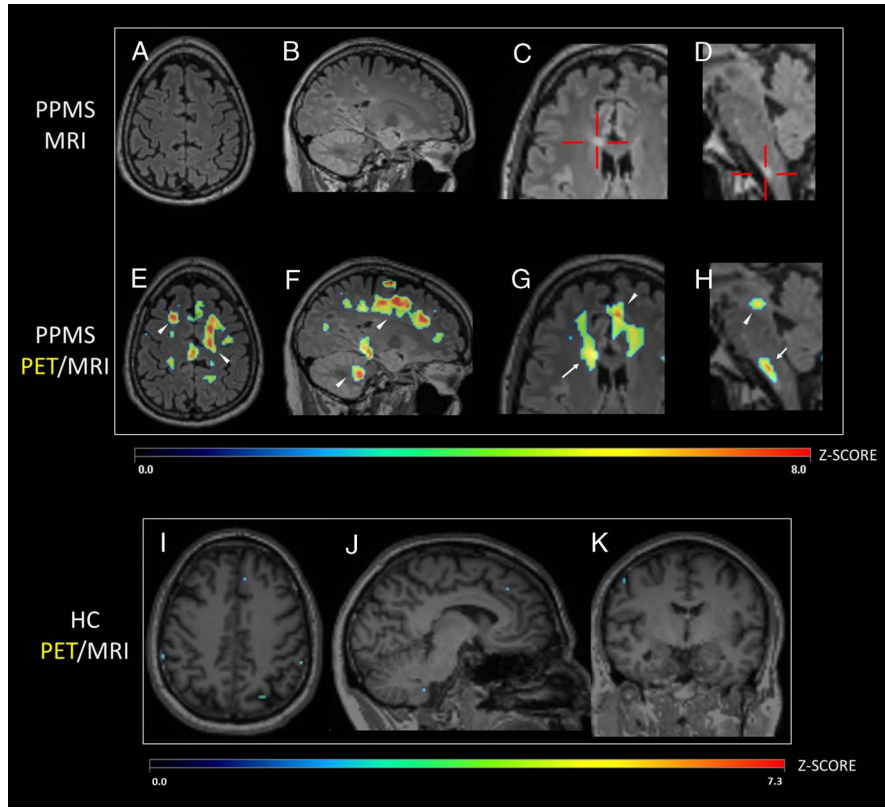

FIGURE 1. Widespread glial activation in a primary progressive multiple sclerosis (PPMS) patient with few lesions on MRI. Transverse and sagittal fluid-attenuated inversion recovery MRI slices of a 64-year-old PPMS patient show normal-appearing white matter (NAWM) (**A**, **B**) except for a few fluid-attenuated inversion recovery bright lesions (**C**, **D**, crosshairs), which are seen in right periventricular white matter (WM) and medulla. *Z*-score maps of increased ^{18}F-PBR06 PET uptake (thresholded at $z > 4.0$) superimposed on MRI (**E**–**G**) reveal widespread increased radiotracer uptake in NAWM (arrowheads). Additionally, there is focal increased uptake corresponding to a right periventricular WM lesion (**G**, arrow) and in a perilesional area in the medulla (**H**, arrow). A focal area of increased ^{18}F-PBR06 uptake in the midbrain (**H**, arrowhead) has no corresponding MRI abnormality (**D**). In contrast, an age- and genotype-matched healthy control (HC) shows no significant clusters of voxels with increased radiotracer uptake (**I**–**K**). The PPMS patient and HC are both medium-affinity binders for rs6971 polymorphism[1] known to affect the ligand's binding to the translocator protein (TSPO) on activated microglia and astrocytes. Approximately 10% to 15% of patients with multiple sclerosis (MS) present with the primary progressive phenotype of the disease, clinically characterized by gradually progressive symptoms from disease onset.[2] Pathologically, diffuse microglial activation and astrocytosis are characteristic of PPMS but are not detected by routine MRI.[3] Similarly, PPMS patients have higher proportions of mixed active/inactive lesions with perilesionally accumulated activated microglia on pathological examination, which are also not seen on routine MRI.[4] This case supports the ability of ^{18}F-PBR06 PET to reveal neuroinflammation in NAWM in absence of MRI abnormalities and in lesional and perilesional WM, consistent with neuropathology in PPMS. ^{18}F-PBR06 is a second-generation TSPO PET ligand that has been shown to represent increased glial (including microglial and astrocytic) activation in various disease states and disease models, including MS.[5,6] Other TSPO PET ligands such as ^{11}C-PK11195 and ^{11}C-PBR28 have been shown to detect neuroinflammatory aspects of white and gray matter pathology in MS,[5] but TSPO PET has not been extensively studied in PPMS.[5,7] ^{18}F-PBR06 has the advantage of a longer radiotracer half-life and better signal-to-noise ratio, as compared with ^{11}C-labeled TSPO ligands. No previous cases of glial activity in PPMS using ^{18}F-PBR06 PET have been reported. While aging can be associated with increased glial activity, the age- and genotype-matched HC (**I**–**K**) demonstrated no significant clusters of voxels with increased ^{18}F-PBR06 uptake. Further, despite the cumulative evidence on the role of TSPO PET imaging in MS,[5,7] individualized approaches for TSPO PET image analyses have been overlooked. In comparison, individualized parametric 3-dimensional *z*-score mapping, based on comparison to HC database, has been utilized for brain ^{18}F-FDG PET imaging and has been shown to improve the diagnostic accuracy in clinical circumstances, for example, in detecting patients with mild cognitive impairment and Alzheimer's disease.[8] This case demonstrates that short-duration, static ^{18}F-PBR06 PET imaging can demonstrate widespread increased glial activation in PPMS using a clinically feasible, individualized *z*-score mapping approach, similar to the approaches used in ^{18}F-FDG PET literature. Further studies of ^{18}F-PBR06 in MS are urgently warranted.