Can PET imaging tell us what's the matter with the gray matter in multiple sclerosis?

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In this issue of *Neurology*®, Politis et al.[1] utilized brain PET and the radioligand ^{11}C-PK11195 to estimate expression of the translocator protein 18 kD (TSPO) as a marker of activated microglia in a cohort of 18 patients with multiple sclerosis (MS) and 8 healthy controls. In patients with MS, they found that increased PK11195 binding in the cortical gray matter (GM), but not white matter (WM), correlated with Expanded Disability Status Scale (EDSS) scores ($r = 0.54$). Remarkably, the simple partial correlation coefficient for GM signal and EDSS score in the secondary progressive MS (SPMS) cohort (n = 8) was $r = 0.84$, whereas there was no relationship in patients with relapsing-remitting MS (RRMS). GM PK11195 binding values did not correlate with duration of disease. Interestingly, the binding patterns suggested regional pathology, with RRMS patients having more binding in the postcentral, middle frontal, anterior orbital, fusiform, and parahippocampal gyri, and patients with SPMS additionally having more binding in the precentral, superior parietal, lingual and anterior superior, and medial and inferior temporal gyri, as compared to controls. The precentral gyrus binding values were associated with EDSS in SPMS ($r = 0.9$), whereas only postcentral binding values correlated with EDSS in RRMS ($r = 0.73$). No associations were found between GM binding and cortical volume or WM binding and clinical disability scores.

The present study represents an exciting technical advance in our ability to image activated immune cells in vivo and provides more support for the clinical relevance of GM pathology in MS. While cortical GM pathology in MS was recognized many decades ago pathologically, GM lesions are not seen well on conventional MRIs, and this led to an underestimate by neurologists of the role of GM injury, until recently.[2,3] Quantitative MRI analyses of cortical GM and WM volumes in patients with MS have revealed that the GM atrophies at least as quickly as WM and that GM atrophy accelerates in the secondary progressive stage of the disease.[4] There may be multiple mechanisms underlying this process, including secondary effects of WM injury with dying back effects on neurons, as well as a direct immune-mediated attack on gray matter.[5] Indeed, there are now numerous reports of meningeal foci of lymphoid aggregates, and a recent pathology report confirmed active demyelination in cortical tissues obtained en passant during needle biopsy of tumefactive white matter lesions in persons ultimately diagnosed with early cases of MS.[5,6] Activated macrophages and microglia have been well described in the GM pathologic specimens, but in vivo imaging of these cell types has been limited.

TSPO is expressed on activated macrophages and microglia and has been studied as a potential in vivo biomarker of these cells. Unfortunately, precise quantification of the ^{11}C-PK11195 PET brain signal as a TSPO biomarker has been challenging due to multiple factors, including the lack of a good brain reference or comparison region, binding to astrocytes, and significant TSPO density in the brain vasculature in smooth muscle and endothelial cells.[7] Although the authors used optimized modeling and brain segmentation procedures to overcome some of the limitations, their kinetic modeling method remains dependent on assumptions of vascular tracer activity that may be different in an inflammatory disease like MS compared to healthy controls. The cortical binding signal may also be confounded by subpial vascular activity given the limited spatial resolution of PET. Furthermore, the main PK11195 binding measure was in part weighted by total GM volume (more atrophic in SPMS). Future studies are needed to control for regional cortical thickness and blood flow and assess the test-retest reliability of PK11195 PET in MS.

Beyond the technical aspects of PET imaging, limitations of this study include the small sample size and cross-sectional nature of the study. Longitudinal studies of how GM binding patterns change over

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time will be necessary to further our understanding of the likely complex relationship between macrophage and microglial activation and tissue injury. Indeed, the lack of a direct correlation between GM PK11195 signal and GM volume is not surprising since there may be a temporal lag between cellular activation and the subsequent tissue injurious effects that result in loss of compartmental volume detected by MRI. Furthermore, it has not been definitively established that all activated macrophages and microglia are pathogenic and, in fact, some subsets of these cells have been shown to have protective effects. For example, M2 macrophages, characterized by arginase production, have been linked with both immune regulatory properties and decreased tissue damage via release of nitric oxide and reduced reactive oxygen species.[8] Macrophages also likely play a critical role in phagocytic clearance of myelin debris. Similarly, while activated microglia have the capacity to be injurious to CNS tissues, they also promote synaptic stripping, which may serve a neuroprotective role in GM by physically removing inhibitory GABAergic synaptic input, which promotes NMDA receptor activity and neuronal survival.[9]

Nonetheless, the present study is an important step forward and suggests a crucial role of activated microglial and macrophages in GM pathology in MS. Future studies are required to understand more completely the relationship between the TSPO signal and resulting GM atrophy and disability, which may ensue years later. Encouragingly, one recent longitudinal study was able to see a decrease in GM PK11195 signal a year after initiating MS immunomodulating therapy in a cohort of 9 patients with RRMS.[10] Even more specific ligands that could provide information regarding immune cell phenotypes in the CNS could lead to additional critical understanding of the mechanisms underlying GM inflammation in MS, and therefore aid in prognosis and monitoring of therapeutic interventions.

DISCLOSURE

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