Do slowly expanding lesions correspond to chronic active multiple sclerosis lesions? An integrated imaging analysis study

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Abstract

Chronic active lesions (CALs) are a hallmark of multiple sclerosis (MS) pathology, associated with extensive tissue damage, disability progression, and overall disease burden. Histopathologically, they consist of a hypocellular core surrounded by a rim of iron-laden, chronically activated microglia/macrophages. Proposed magnetic resonance imaging (MRI) biomarkers of CALs are paramagnetic rim lesions (PRLs) or slowly expanding lesions (SELs), detected respectively on susceptibility-based images or on longitudinal conventional MRI. While PRLs are histopathologically validated *in vivo* correlates of CALs, SELs lack pathological validation. In this study, we examine the relationship between SELs and PRLs and evaluate the robustness of the SEL detection algorithm in 56 MS participants, all imaged using a strictly homogeneous protocol on the same 3T scanner for three consecutive timepoints. PRLs included distinct subgroups of both shrinking and expanding lesions ($p < 0.001$), challenging the assumption that CALs necessarily expand over time. SEL detection demonstrated instability across different input resolution and segmentation methods, yielding a mean dice similarity score of 0.375. In random forest analysis, SEL volume showed inconsistent and weaker predictive value for MS disability and severity (EDSS, MSSS) compared to PRL volume. Critically, lesion-level overlap between SELs and PRLs was negligible (Cohen's $\kappa = -0.022$) once corrected for overlap by chance. Taken together, our findings indicate that SELs and PRLs are essentially independent, underscoring the need for a refined longitudinal volumetric definition to establish a reliable CALs' biomarker.

Keywords: Multiple Sclerosis, MRI, Chronic active lesions, paramagnetic rim lesions, slowly expanding lesions