Transcortical Inflammation and Expanding Cortical Demyelination in Progressive MS

Short title: Transcortical Perivascular Inflammation in MS

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Background
Cortical plaques are hallmarks of primary (PPMS) and secondary progressive (SPMS) multiple sclerosis but their activity/expansion in relation to perivascular mononuclear/lymphocytic infiltrates (PMI's) are unknown.

Methods
We performed large-area microscopy in twelve post-mortem patients with PPMS, 14 with SPMS and 22 controls in brain sections stained with (haematoxylin-eosin) HE and luxol-fast blue (LFB). We summarized per-patient PMI densities (#/cm^2 cortical tissue, #/cm length of meninges) and size scores (semi-quantitative scale), based on rows and numbers of inflammatory cells, in intracortical, meningeal, and juxtacortical compartments. CD3+ T-cells and CD20+ B-cells were investigated and confirmed in PMI's in 10 patients. In two patients vs. two controls, we investigated and found IgG-deposition in cortical plaques corroborating adaptive immune activation. In PLP-stained sections, we measured area percentages of total cortical plaque and pooled "active" (CD68+ macrophage-filled) and "slowly expanding" (SE; CD68+ microglia-rims), into "active/SE" areas. Blinded chart review determined clinical courses.

Results
PMI sizes and densities inter-related closely in juxta-cortical and meningeal compartments. Active/SE areas correlated with PMI sizes in all three compartments. By contrast, total cortical plaque correlated weakly and only with meningeal PMI density.
In PPMS (not SPMS), "active/SE" areas and PMI sizes (intra- and juxta-cortical) correlated with shorter disease and progressive phase durations. Also, total plaque load correlated with the latest EDSS.

Conclusions
Trans-cortical inflammatory flares of large PMI's rather than persisting densities of smaller PMI's may be involved in cortical plaque expansion and, in PPMS, severe trajectories.