NEUROINFLAMMATION IN MULTIPLE SYSTEM ATROPHY IS INFLUENCED BY PATHOLOGICAL ALPHA-SYNUCLEIN AGGREGATES

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Introduction: Multiple system atrophy (MSA) closely resembles Parkinson’s disease (PD) clinically, but with a range of autonomic signs. However, unlike PD that displays primarily neuronal pathology, MSA exhibits widespread astrogliosis and the occurrence of α-synuclein (α-syn) glial cytoplasmic inclusions (GCIs) in mature oligodendrocytes. To investigate the relationship between α-syn inclusions and neuroinflammation in MSA, we conducted quantitative morphometric analysis on MSA cases, and cell culture and animal model studies. Methods: Using Imaris software, we obtained “skinned” three-dimensional models of GFAP-positive astrocytes in MSA and normal tissue (n = 75) from confocal z-stacks and measured the astrocyte process length and thickness and radial distance to GCI. Results: Astrocyte activation results in highly ramified astrocyte morphology with extended and thickened processes. Astrocytes proximal to GCI-containing oligodendrocytes (r < 25 μm) had significantly (p, 0.05) longer and thicker processes than distal astrocytes (r > 25 μm), with a reciprocal linear correlation (m, 90 μm²) between mean process length and radial distance to the nearest GCI (R², 0.7). In primary cell culture studies, α-syn addition caused ERK-dependent activation of rat astrocytes and perinuclear α-syn inclusions in mature (MOSP-positive) rat oligodendrocytes. Activated astrocytes were also observed in close proximity to α-syn deposits in a unilateral rotenone-lesion mouse model. Moreover, unilateral injection of MSA tissue-derived α-syn into the mouse medial forebrain bundle resulted in widespread neuroinflammation in the α-syn-injected, but not sham-injected hemisphere. Conclusion: Taken together, our data suggests that localized extracellular concentrations of α-syn may underlie astrocyte and oligodendrocyte MSA pathological features. (248 words).