Disruption of glymphatic system and slow in waste clearance in the SOD1-G93A mouse model of ALS

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Amyotrophic lateral sclerosis (ALS) is a motor neuron specific neurodegenerative disease. Accumulation of mutant Cu/Zn-superoxide dismutase (SOD1) protein aggregate in the spinal motor neurons is a common pathological hallmark in several types of ALS animal models and patients. The glymphatic system is a waste clearance system in the central nervous system: the cerebrospinal fluid (CSF) flow through the perivascular space into interstitial spaces and the perivascular localization of aquaporin-4 (AQP4) promote its directional flow and waste clearance. We aimed to show involvement of glymphatic system in disease progression of ALS. We found AQP4 deficiency in SOD1-ALS mice accelerated disease onset and shortened survival period. In addition, abnormal SOD1 protein deposition was increased in SOD1-ALS/AQP4 knockout mice and the clearance of the protein from the spinal cord was slowed in AQP4 knockout mice. Furthermore, we observed AQP4 overexpression and mislocalization and detected glymphatic disfunction in ALS model mice for the first time. We suggest that the aberrant AQP4 distribution in the ALS model mice disrupts directional CSF flow and accelerates accumulation of abnormal proteins in the spinal cord. Our study would provide a new insight on improving the glymphatic system in ALS treatment strategies.