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Involvement of glymphatic system in amyotrophic lateral sclerosis pathology

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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 directional flow of the cerebrospinal fluid (CSF) through the perivascular into interstitial spaces and the perivascular localization of aquaporin-4 (AQP4) promote its directional flow. Previously we reported that the AQP4 localization is aberrant and its expression is highly upregulated in SOD1-ALS mice during the progression of ALS symptoms (Watanabe et al., Neurosci Res, 133, 48-57, 2017). In the present study, we found the increase in the abnormal SOD1 protein deposition in SOD1-ALS/AQP4 knockout mice and the clearance of the protein from the spinal cord was slowed in AQP4 knockout mice. When we injected fluorescent labeled ovalbumin into the cisterna magna, the solute accumulation was greater in the SOD1-ALS mice than that in the wild-type mice. Our study suggests that the aberrant AQP4 distribution in the ALS model mice disrupts directional CSF flow and accelerates accumulation of toxic proteins in the spinal cord.