Does neuroinflammation sustain neurodegeneration in ALS?

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Amyotrophic lateral sclerosis (ALS), the most prevalent type of motor neuron disease in adults, affecting 4–6 per 100,000, is a fatal neurodegenerative disease. ALS is characterized by the degeneration of both upper motor neurons comprising the corticospinal tract and lower motor neurons arising from the brainstem nuclei and ventral roots of the spinal cord. The only drug approved for ALS—riluzole—provides a modest survival benefit. An improved understanding of the pathophysiology of ALS has potential for the development of more effective therapeutic interventions.

The death of neurons in ALS is accompanied by a neuroinflammatory response that is characterized by microglial activation and T-cell infiltration in affected regions.[1] However, an understanding of inflammation in ALS, as harmful, protective, or both, is elusive. Microglia represent the first line of defense in the CNS, and is the first cell type to be activated in case of injury. Microglial activation may be cytotoxic in ALS, particularly late in the disease process.[1,2] Further, activated microglia might have a protective role in CNS injury, including motor neuron death, through the release of anti-inflammatory cytokines and growth factors.[1] Understanding the relationships between neurodegeneration and neuroinflammation in ALS is thus critical if they are to be harnessed for therapeutic purposes.

Over the last 2 decades, structural, functional, and molecular neuroimaging findings have changed our understanding of the pathophysiology of ALS,[3,4] by providing the means to visualize in vivo the propagation of pathology. Activated microglia are characterized by high expression of the 18 kDa translocator protein (TSPO), formerly known as the peripheral benzodiazepine receptor (PBR), on mitochondria, and PET radiotracers binding to TSPO allow an in vivo assessment of microglia activation in the brain. The first application of TSPO PET in patients with ALS showed increased binding in the motor cortex, pons, dorsolateral prefrontal cortex, and thalamus, where the extent of microgliosis was positively correlated with the severity of ALS.[5] Increased TSPO expression was subsequently reported in the primary motor cortex, supplementary motor area, as well as temporal cortex of patients with ALS, giving support to a role for inflammatory processes in ALS.[6,7] This piece of evidence is strengthened by the findings that myo-inositol, a spectroscopic marker of glial activity, is increased in the primary motor cortex of patients with ALS.[8]

In this issue of *Neurology*®, Alshikho et al.[9] elegantly use a combination of MRI and PET techniques to help advance our understanding of the role of glial cells in ALS pathogenesis. In 10 patients with ALS, the authors interrogated the relationship between glial activation, measured by [^{11}C]-PBR28 PET, and the location of structural brain abnormalities, measured by diffusion tensor MRI and cortical thickness. Increased expression of the glial marker [^{11}C]-PBR28 colocalized with reduced fractional anisotropy (FA) in the upper part of the corticospinal tract and with cortical thinning of the precentral gyrus. Moreover, increased [^{11}C]-PBR28 in the left motor cortex correlated with FA reduction and cortical thinning. All 3 measures ([^{11}C]-PBR28, FA, and cortical thickness) were strongly associated with clinical upper motor neuron impairment.

Although limited by the small number of patients and by the relatively advanced disease in some of them, this study provides in vivo a link between disease mechanisms (gliosis and inflammation) and structural alterations (cortical thinning and white matter changes). The main unanswered question, however, is whether the structural brain abnormalities are the consequence or the cause of the neuroinflammation. Longitudinal studies are warranted to address the temporal sequences of events and to explore whether the assessment of microglial activation can help to predict the pattern of pathologic spreading in ALS. Longitudinal, multimodal neuroimaging studies of presymptomatic individuals carrying ALS-related mutations would offer an unprecedented opportunity to determine the order and rate of brain changes in the presymptomatic stage of the disease.[10] Together with the findings by Alshikho et al.,[9] these future studies would clarify whether therapeutic modulation of the inflammatory response could provide an opportunity to alter disease progression in ALS.

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Another important but still unexplored issue hinders translation into clinical application, i.e., whether [^{11}C]-PBR28 PET is sufficiently sensitive to detect change over time. Future studies will need to determine its potential as a robust pharmacodynamic marker to monitor in vivo the efficacy of treatments targeting neuroinflammation in ALS, not only at the group level but more critically in individual patients.

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REFERENCES

1. Evans MC, Couch Y, Sibson N, Turner MR. Inflammation and neurovascular changes in amyotrophic lateral sclerosis. Mol Cell Neurosci 2013;53:34–41.
2. Boillee S, Yamanaka K, Lobsiger CS, et al. Onset and progression in inherited ALS determined by motor neurons and microglia. Science 2006;312:1389–1392.
3. Chiò A, Pagani M, Agosta F, Calvo A, Cistaro A, Filippi M. Neuroimaging in amyotrophic lateral sclerosis: systematic insight into structural and functional changes. Lancet Neurol 2014;13:1228–1240.
4. Filippi M, Agosta F, Grosskreutz J, et al. Progress towards a neuroimaging biomarker for amyotrophic lateral sclerosis. Lancet Neurol 2015;14:786–788.
5. Turner MR, Cagnin A, Turkheimer FE, et al. Evidence of widespread cerebral microglial activation in amyotrophic lateral sclerosis: an [11C](R)-PK11195 positron emission tomography study. Neurobiol Dis 2004;15:601–609.
6. Corcia P, Tauber C, Vercoullie J, et al. Molecular imaging of microglial activation in amyotrophic lateral sclerosis. PLoS One 2012;7:e52941.
7. Zurcher NR, Loggia ML, Lawson R, et al. Increased in vivo glial activation in patients with amyotrophic lateral sclerosis: assessed with [(11)C]-PBR28. Neuroimage Clin 2015;7:409–414.
8. Kalra S, Hanstock CC, Martin WR, Allen PS, Johnston WS. Detection of cerebral degeneration in amyotrophic lateral sclerosis using high-field magnetic resonance spectroscopy. Arch Neurol 2006;63:1144–1148.
9. Alshikho MJ, Zürcher NR, Loggia ML, et al. Glial activation colocalizes with structural abnormalities in amyotrophic lateral sclerosis. Neurology 2016;87:2554–2561.
10. Turner MR, Hammers A, Al-Chalabi A, et al. Distinct cerebral lesions in sporadic and 'D90A'SOD1 ALS: studies with [11C]flumazenil PET. Brain 2005;128:1323–1329.