Hyperexcitability and amyotrophic lateral sclerosis

Matthew C. Kiernan, PhD, DSc, FRACP
Susanne Petri, MD

Correspondence & reprint requests to Prof. Kiernan: M.kiernan@unsw.edu.au

Neurology® 2012;78:1544–1545

Although amyotrophic lateral sclerosis (ALS) was described some 150 years ago, there remain critical questions about the origin and progression of the disease. A recent focus of clinical research has been the potential role of excitotoxicity underlying the pathophysiology of ALS.[1] Several strands of evidence indicate that a net increase in excitatory neurotransmission in ALS results from reduced cortical inhibition. In this issue of *Neurology*®, Foerster and colleagues[2] add a further piece to this complex pathophysiologic puzzle, by identifying differences in γ-aminobutyric acid (GABA) content in the motor cortex of patients with ALS. Specifically, using a novel magnetic resonance spectroscopy approach, they found reduced cortical GABA in patients with ALS compared to controls. This in vivo characterization of GABA levels in patients with ALS supports the emerging evidence for cortical hyperexcitability in patients with sporadic and familial ALS. The data are also relevant to the urgently needed development of disease-specific biomarkers: while EMG is more sensitive than clinical examination for the detection of lower motor neuronal involvement, a robust biomarker is lacking that may identify subclinical upper motor neuron degeneration and thereby facilitate an early diagnosis of ALS.

These advanced neuroimaging findings[2] complement a range of recent clinical and functional approaches, including longitudinal studies that have identified the development of cortical hyperexcitability in asymptomatic carriers of mutations linked to ALS. Specifically, cortical hyperexcitability, as determined by reduction in short interval intracortical inhibition, appears to develop prior to the clinical onset of ALS.[3] These findings support the hypothesis that ALS, or at least subtypes of this clinically and pathophysiologically heterogeneous disorder, may be viewed primarily as a neurodegenerative brain disorder involving cortical motor neurons that synapse with anterior horn cells. Dysfunction of these neurons has been postulated to result in alterations of glutamine metabolism and thereby anterior horn cell destruction by means of an anterograde degenerative process.[4] Such a dying-forward hypothesis may also explain the clinical observations that the oculomotor, abducens, and Onuf motor nuclei are typically spared in ALS, given that these structures all lack direct cortical motor neuron connections.

Reduced intracortical inhibition may reflect a loss of inhibitory interneurons or alteration in the expression pattern of postsynaptic inhibitory receptors in the ALS cortex. Release of the inhibitory neurotransmitter GABA is largely a function of interneurons, at both cortical and spinal levels, exerting a regulatory role over neuronal excitation of neurons and their networks. Recent work on ALS pathogenesis suggests a critical and intrinsic role of interneurons.[5] For instance, immunohistocytochemical studies have identified alterations in the ratio of GABA to glycine receptors in disease-susceptible motor nuclei of the brainstem of patients with ALS, likely to be secondary to presynaptic interneuron pathology. Histologic studies have identified reduction of $GABA_A$ receptor subunit mRNA expression not only in the ALS motor cortex, but also in extramotor frontal and temporal brain regions.[6,7] This is particularly topical, given the emerging overlap of ALS and frontotemporal dementia, combined with the recent discovery of mutations in chromosome 9 that underlie a large proportion of familial ALS and frontotemporal dementia (FTD), in addition to apparently sporadic disease.[8]

Short interval intracortical inhibition is mediated by GABA-secreting inhibitory interneurons that act via $GABA_A$ receptors.[9] Reduction in SICI may develop through loss of cortical inhibitory interneurons, combined with glutamine-mediated downregulation. This hypothesis is further supported by findings in the SOD1 mouse model, whereby degeneration of spinal motor neurons appeared secondary to dysfunction within central motor pathways.

See page 1596

From the Prince of Wales Clinical School (M.C.K.), University of New South Wales, and Neuroscience Research Australia, Sydney, Australia; and Department of Neurology (S.P.), Hannover Medical School, Hannover, Germany.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this editorial.

Supportive findings from neuroimaging approaches are now emerging. Functional PET imaging studies have identified widespread loss of binding of the $GABA_A$ receptor ligand flumazenil in patients with sporadic ALS, again consistent with the loss of inhibitory influence.[5] Multimodal MRI, integrating structural and fMRI data, suggests a loss of cortical transcallosal inhibition due to white matter damage, potentially associated with a reduction of GABAergic interneurons, and, at the same time, an increase in functional connectivity.[10]

Magnetic resonance spectroscopy (MRS) further supports the study from Foerster and colleagues.[2] While MRS has been utilized to study neurometabolic changes in ALS, the novel 3-Tesla proton MRS technique has enabled quantification of the cortical GABA content in vivo. This innovative approach now needs to be applied to a larger patient cohort, ideally with longitudinal measurements in the same patients, to understand whether reduction in cortical GABA levels can be correlated with specific ALS phenotypes, particularly the degree of upper motor neuron involvement, or with disease progression. Such data will provide further insight as to whether cortical GABA content is a prognostic marker or reflects effects of therapeutic interventions in clinical trials. In the context of emerging evidence about the clinical, genetic, and pathologic overlap between ALS and FTD, MRS GABA measurements in cortical regions other than the primary motor cortex might further facilitate in vivo assessment of extramotor involvement in patients with ALS.

It is apparent that a wide spectrum of clinical investigative approaches are identifying loss of inhibitory function at the heart of ALS. In vivo quantification of the main inhibitory neurotransmitter in the CNS may therefore facilitate the development of a clinically useful biomarker, suitable for more sensitive detection and monitoring of upper motor neuron involvement and for the study of pathologic alterations in cortical regions beyond the motor system. More importantly, it is perhaps now time to devise novel therapeutic approaches, aiming to restore the inhibitory balance and thereby promote neuronal repair in ALS.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. Lancet 2011;377:942–955.
2. Foerster BR, Callaghan BC, Petrou M, et al. Decreased motor cortex γ-aminobutyric acid in amyotrophic lateral sclerosis. Neurology 2012;78:1596–1600.
3. Vucic S, Nicholson G, Kiernan MC. Cortical hyperexcitability may precede the onset of familial amyotrophic lateral sclerosis. Brain 2008;131:1540–1550.
4. Eisen A, Pant B, Stewart H. Cortical excitability in amyotrophic lateral sclerosis: a clue to pathogenesis. Can J Neurol Sci 1993;20:11–16.
5. Turner MR, Kiernan MC. Does interneuronal dysfunction contribute to neurodegeneration in amyotrophic lateral sclerosis? Amyotroph Lateral Scler Epub 2012 Mar 16.
6. Petri S, Krampfl K, Hashemi F, et al. Distribution of GABAA receptor mRNA in the motor cortex of ALS patients. J Neuropathol Exp Neurol 2003;62:1041–1051.
7. Petri S, Kollewe K, Grothe C, et al. GABA(A)-receptor mRNA expression in the prefrontal and temporal cortex of ALS patients. J Neurol Sci 2006;250:124–132.
8. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 2011;72:257–268.
9. Vucic S, Kiernan MC. Novel threshold tracking techniques suggest that cortical hyperexcitability is an early feature of MND. Brain 2006;129:2436–2446.
10. Douaud G, Filippini N, Knight S, et al. Integration of structural and functional magnetic resonance imaging in amyotrophic lateral sclerosis. Brain 2011;134:3467–3476.