RESEARCH LETTER

Longitudinal Cortical Atrophy in Amyotrophic Lateral Sclerosis With Frontotemporal Dementia

Frontotemporal dementia (FTD) with amyotrophic lateral sclerosis (ALS) presents with impaired language or behavior and declining motor function. Frontotemporal lobar degeneration with ubiquinated transactivating responsive sequence DNA-binding protein (TDP-43) inclusions is found postmortem in the affected brain areas of patients with ALS, FTD/ALS, and many patients with FTD.1 Prior magnetic resonance imaging (MRI) observations revealed cross-sectional atrophy in the motor and/or premotor cortices of patients with FTD/ALS,2 while a longitudinal study using diffusion tensor imaging revealed corticospinal tract changes.3 We used high-resolution diffeomorphic image normalization and serial MRI to provide the first assessment of longitudinal cortical atrophy in patients with FTD/ALS relative to controls.

Methods. Subjects. We contrasted 4 elderly controls with 4 patients with FTD/ALS, performed by an experienced neurologist (M.G.) at the University of Pennsylvania Department of Neurology. Two trained reviewers (M.G. and L.M.) of a consensus committee confirmed the presence of specific diagnostic criteria based on an independent review of the semistructured history, detailed mental status examination, and complete neurological examination. These patients and their legal representatives participated in an informed consent procedure approved by the institutional review board at the University of Pennsylvania. The age-matched (P < 0.1) patients (mean [SD] age, 61.3 [6.1] years) were right-handed, high school-educated (mean [SD] education, 17.5 [1.9] years), native English speakers with a mean (SD) Mini-Mental State Examination score at the first examination of 27.0 (3.2). The second evaluation was conducted a mean (SD) of 5.3 (0.5) months after the first evaluation, and the mean (SD) score at the second evaluation was 21.3 (8.5).

Imaging. Baseline and follow-up image acquisitions (Trio 3.0T MRI scanner; Siemens, Munich, Germany) began with a sagittal T1-weighted localizer. A T1 structural axial image was acquired with a repetition time of 1620 milliseconds; TE echo time, 3 seconds; slice thickness, 1 mm; in-plane resolution, 0.9766 mm × 0.9766 mm; and field of view, 256 × 256 × 192 voxels.

Imaging Normalization and Longitudinal Atrophy Assessment. We use a longitudinal extension of large deformation tensor-based morphometry (LDTBM)4 in this study. This framework first generates an unbiased intra-subject measurement of atrophy from each subject's baseline and follow-up image.5 One high-resolution voxelwise map of annual atrophy for each individual is transferred to a local template space that allows statistical contrast of subject and control longitudinal change via the t test, computed within an explicit gray matter mask.

Results. We rendered cortical regions with significant annual atrophy due to FTD/ALS on the local template in the Figure. Significant effects occur in the premotor cortex, primary motor cortex, and parietal lobe bilaterally in Brodmann areas (BA) 4, 6, and 7. The average annual cortical atrophy over significant voxels in FTD/ALS on the right and left is 8.5% and 7.6%, respectively, in BA4; 8.1% and 5.9% in BA6; and 3.6% and 2.2% in BA7. For all cortices in FTD/ALS, the atrophy rate was 1.0% per year; in elderly controls, 0.25% per year. The local atrophy rate did not correlate with global brain atrophy; the age and global brain atrophy rates did not correlate.

Comment. We found significant differences in longitudinal cortical atrophy in motor and premotor areas in patients with clinical features of both ALS and FTD. Amyotrophic lateral sclerosis cooccurs with FTD in 5% to 10% of cases. This is owing, in part, to the presence of ubiquitinated TDP-43 underlying both FTD and ALS.6 Presumably, regional motor and premotor cortical atrophy reflect the motor and cognitive changes, respectively, that are characteristic of this condition. Additional study is needed to establish whether there are clinically observable changes corresponding to these parietal changes.
Cortical atrophy is thought to be difficult to detect in ALS because the relatively rapid rate of clinical progression minimizes the opportunity for noticeable cortical atrophy to emerge and motor disease limits the practical limitation of follow-up assessments. This may be the first demonstration of longitudinal cortical atrophy in FTD/ALS because normalization with LDTBM reduces residual intersubject variance in neuroanatomy while retaining sensitivity to intrasubject effects, augmenting detection power in neurormorphometry.

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**Author Contributions:** Dr Grossman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Avants and Grossman. *Acquisition of data:* Khan, McCluskey, and Elman. *Analysis and interpretation of data:* Avants, Khan, and Grossman. *Drafting of the manuscript:* Avants, Khan, and Grossman. *Critical revision of the manuscript for important intellectual content:* Avants, McCluskey, Elman, and Grossman. *Statistical analysis:* Avants. *Obtained funding:* Avants. *Administrative, technical, and material support:* Khan. *Study supervision:* Grossman.

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**COMMENTS AND OPINIONS**

**Motor Nerve Hyperexcitability and Muscle Cramps in Machado-Joseph Disease**

We read the article by França et al with great interest. We thank them for confirming our previous results regarding the high frequency of and disability associated with muscle cramps in a larger sample of patients with Machado-Joseph disease (MJD). We would like to raise some concerns regarding the authors’ interpretation of the findings.

First, França and colleagues proposed that altered excitatory inputs from the corticospinal fibers rather than the peripheral motor axonal changes might be responsible for muscle cramps in MJD. Muscle cramps and fasciculations arise from spontaneous motor unit activities frequently associated with lower motor neuron disorders, and ectopic firing usually originates from the distal motor axons, especially the intramuscular nerve terminals.1 We have shown that muscle cramp severity correlates with an increased index of peripheral axonal excitability, suggesting that cramps in MJD are associated with underlying peripheral axonal loss and resulting collateral sprouting by the surviving neurons. We consider muscle cramp a symptom of motor nerve sprouting but not of neuronal degeneration. In our experience, disabling muscle cramps in patients with MJD are most prominent during the early stages of the disease and then gradually disappear with the progression of amyotrophy.2 This phenomenon would possibly be associated with the high ability of sprouting in the early stages of disease. Therefore, the subgroup of patients without cramps might include patients in the early and advanced stages of MJD. We believe that this fact accounts for the seemingly insignificant difference in the neurophysiological parameters between groups with and without cramps.

Second, França and colleagues showed that the cramp in MJD was effectively treated with carbamazepine. In our previous study,2 patients with MJD who had disabling muscle cramps benefited from mexiletine hydrochloride treatment, and nerve excitability testing suggested that increases in persistent sodium currents in the peripheral motor axons lead to axonal hyperexcitability. Hence, the authors’ use of sodium channel blockers for muscle cramps in MJD appears to be a rational course. Carbamazepine is an effective and inexpensive antiepileptic drug, but serious adverse effects are not rare. Therefore, further studies will be required to investigate which sodium channel blocker is the most appropriate treatment for muscle cramps in patients with MJD.

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In reply

We are very pleased with the comments raised by Kanai and Kuwabara regarding our study. Our findings in the series of Brazilian patients with MJD indeed confirm previous results reported by Kanai et al,1 indicating that muscle cramps are a frequent and disabling manifestation of the disease.