Cortical Atrophy in Experimental Autoimmune Encephalomyelitis

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Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS). A growing body of literature has documented the neurodegenerative aspect of MS[1] and shown gray matter atrophy to be a good indicator of irreversible clinical disease progression and cognitive impairment.[2,3] MRI has been used extensively in the study of the most commonly used animal model of MS, experimental autoimmune encephalomyelitis (EAE).[4] In previous studies we have demonstrated ex vivo gray matter atrophy in the cerebellar cortex of mice with EAE.[5] In this study we proposed to analyze progressive gray matter atrophy in vivo.

Methods

In vivo T2-weighted magnetic resonance images were acquired from 12 C57BL/6 mice, 3 healthy controls and 9 mice with EAE. One set of scans was acquired from each animal prior to disease induction (d0), one set twenty days post disease induction (d20), one set forty days post disease induction (d40) and one set eighty days post disease induction (d80). A minimum deformation atlas (MDA) was constructed from the 48 images collected (Figure 1). The MDA then served as a target space for the spatial and intensity normalization of the original images. Following creation of this atlas the cerebral cortices were manually labeled on the atlas. The labels were then warped onto the spatially normalized images and manually corrected to produce standardized estimates of gray matter volumes in individual subjects.

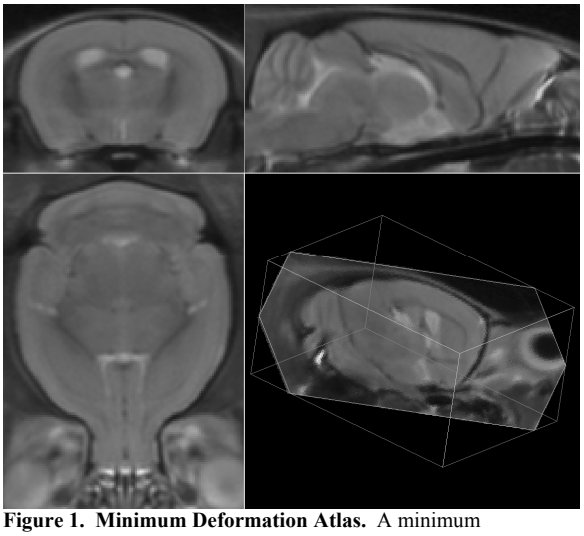

Figure 1. Minimum Deformation Atlas. A minimum deformation atlas was constructed from 48 in vivo high resolution T2-weighted magnetic resonance images of mouse brain, comprising images collected from 12 mice at four time points: before disease induction (d0), twenty days post-induction (d20), forty days post-induction (d40) and eighty days post-induction (d80).

Results

Cerebral cortex volumes of healthy controls and mice with EAE were plotted against disease duration (Figure 2A). In order to quantify the significance of the decreases in cerebral cortex volume observed in individual animals, a repeated-measures ANOVA was peformed to assess the effect of time on cerebral cortex volume in mice with EAE. Cerebral cortex volumes were stable in the control group while gradually decreasing in EAE animals (time x group interaction $p = 0.002$). The volume of the cerebral cortex at eighty days after disease induction (d80) was 71.4 mm^3 (0.8 mm^3) in healthy controls and 68.9 mm^3 (0.8 mm^3) in mice with EAE indicating a 3.5% decrease ($p = 0.04$) in volume. Cerebral cortex volumes of each mouse with EAE were also plotted against disease duration and individual decreases in volume progressed differently in each animal (Figure 2B). These results show that cerebral cortex volume decreases over time in mice with EAE, although the progress of the atrophy varies from mouse to mouse.

Conclusions

We have demonstrated for the first time that atrophy of the cerebral cortex occurs progressively in vivo during autoimmune mediated demyelination. In vivo imaging is more sensitive to changes that occur in neurodegenerative disease models where disease progression varies from one animal to another. Understanding the progression of disease will permit the future design of rational neuroprotective strategies to prevent gray matter atrophy and disability accumulation during EAE, and possibly MS.

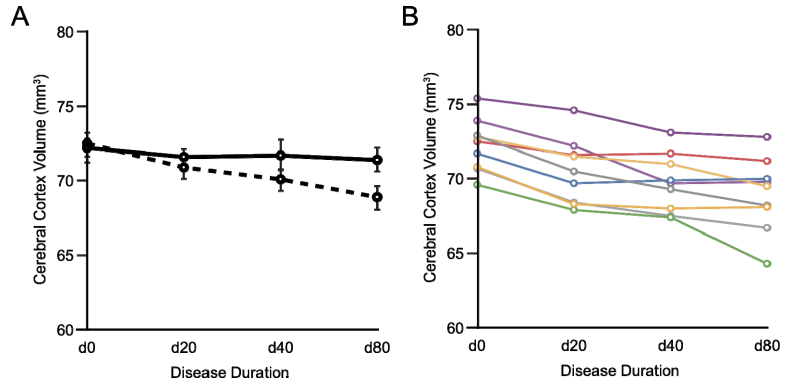

Figure 2. Progressive Gray Matter Atrophy In EAE. (A) A graph of the mean cerebral cortex volume in healthy controls (solid line) and mice with EAE (dashed line) at d0, d20, d40 and d80 plotted against disease duration. (B) A graph of cerebral cortex volume of each individual mouse with EAE measured at d0, d20, d40 and d80 plotted against disease duration. Individual disease courses are represented in differing colors.

References

1. Trapp et al., Curr Opin Neurol 1999
2. Zivadinov et al., Front Biosci 2004
3. Amato et al., Neurology 2009
4. Budde et al., J Neurosci 2009
5. MacKenzie-Graham et al., Neuroimage 2009