Regional Brain Atrophy in Multiple Sclerosis: increasing sensitivity to differences in relapsing-remitting and secondary-progressive disease

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease, with relapsing-remitting (RR) and secondary-progressive (SP) subgroups considered as different phases in the progression of the disease. Pathologic and imaging studies suggest that the development of permanent neurologic impairment in MS is associated with progressive brain and spinal cord atrophy, and atrophy has been suggested as a potential marker of disease progression. Nevertheless, despite differences in the pathological progression of the disease, it has been difficult to establish significant differences between RR and SP groups in measures of the rate of global brain atrophy or ventricular growth [1,2,3].

We therefore hypothesized that the progression of brain atrophy in RR and SP MS may differ in the relative rates of the regional atrophy and their relative contributions to global atrophy.

Methods

Data: Longitudinal atrophy quantification was performed using T1-weighted MR images of the brain obtained from a 1.5T Philips Gyroscan ACS II (Philips Medical Systems, Best, The Netherlands). Forty-six pairs of images from 21 RR patients, and 18 pairs of images from 10 SP patients were used. Patients were selected from the Multiple Sclerosis Clinic of the Montreal Neurological Hospital, and were untreated and at least 1 month post-attack at the time of imaging.

Atrophy Quantification: Longitudinal atrophy was assessed using SIENA [4]. Briefly, the brain and skull are extracted from a pair of MR images. The two brain images are registered, constraining the registration scaling with the skull images. The first brain image is subject to a 2-class (brain/non-brain) segmentation which facilitates brain tissue edge detection in the first brain image. Local intensity gradients are measured, and are used to calculate both search ranges and directions in order to establish the edge motion between the two images. The mean surface motion between the two images is related to the change in brain volume, allowing the calculation of percent brain volume change (PBVC). This method has been previously shown to have a median absolute error of 0.2%.

To extend the SIENA algorithm to obtain regional atrophy measures, a ventricle mask was created by manually segmenting the mean surface motion between the two images. The two brain images are registered, constraining the edge motion between the two images. The rate of atrophy of the entire brain without the ventricular region is calculated as the ratio of PBVC of entire brain without the ventricular masked region)/(time elapsed between scans); and rate of peripheral brain atrophy pVA=(PBVC within the ventricular masked region)/(time elapsed between scans); and rate of peripheral brain atrophy PA=(PBVC of entire brain without the ventricular masked region)/(time elapsed between scans).

Statistics: For subjects with more than 1 pair of scans, atrophy measures were calculated on consecutive pairs, and averaged to ensure independence. Between-group differences in rate of PBVC were assessed using the Wilcoxon rank sum test, within-group differences were assessed using the Wilcoxon signed rank test.

Results

The figure shows a representative T1-weighted image from an MS patient. Superimposed are both those edges used to calculate pVA (white lines surrounding the ventricles), and those edges used to calculate PA (white lines surrounding the cortical surface).

SPs were found to have significantly faster pVA compared to RRs (Table). The PA and GA were not found to be significantly different between the groups, due to higher variance in the RR group for those atrophy measures which include the peripheral brain.

Table: Medians and Interquartile Ranges of Brain Atrophy Rates

<table>
<thead>
<tr>
<th></th>
<th>GA (%/yr)</th>
<th>pVA (%/yr)</th>
<th>PA (%/yr)</th>
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<tbody>
<tr>
<td>RR</td>
<td>2.92</td>
<td>3.06</td>
<td>1.73</td>
</tr>
<tr>
<td></td>
<td>0.15→17.92</td>
<td>0.15→8.93</td>
<td>-1.2→11.50</td>
</tr>
<tr>
<td>SP</td>
<td>13.19</td>
<td>9.68</td>
<td>6.39</td>
</tr>
<tr>
<td></td>
<td>2.83→72.36</td>
<td>2.06→58.81</td>
<td>2.40→35.4</td>
</tr>
<tr>
<td>p</td>
<td>0.29</td>
<td>0.03</td>
<td>0.25</td>
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</table>

We have shown that there is a significant difference between the PA and GA, with the PA being significantly slower than the GA (p=0.011), perhaps indicating that peripheral atrophy is playing a larger role in the global atrophy process.

Conclusion

We have shown that there is a significant difference in the nature of the progression of brain atrophy in RR and SP groups. SP patients have a significantly faster rate of peri-ventricular atrophy than RR patients, suggesting a greater relative volume change along the long projection tracts. The rate of peripheral and global atrophy, which include cortical grey matter, also tended to be higher in the SP group, although not achieving statistical significance due to high variance in the RR group. Furthermore, the difference between the rate of peripheral atrophy and global atrophy in SPs is significantly weaker than in RRs. This suggests that global atrophy and peripheral atrophy are less distinct processes in SPs than in RRs, and that peripheral atrophy may have an increased contribution to global atrophy in SP than in RR.

The increased sensitivity of regional atrophy measures to differences in clinical course, suggests that brain atrophy may not be a uniform process and that regions may have distinct responses to disease progression. Furthermore, these findings suggest that an automatic method of obtaining measures of regional brain atrophy may increase the sensitivity to disease progression. This may be particularly applicable to drug trials with large data sets and which require objective measures to monitor disease progression.

References