Survey of the distribution of lesion size in multiple sclerosis: implication for the measurement of total lesion load

Liqun Wang, H-M Lai, A J Thompson, D H Miller

Abstract

Objectives—Quantitative measurement of lesion load on proton density or T2 weighted brain MRI in multiple sclerosis is a widely used marker of disease progression in treatment trials and natural history studies. However, it has proved difficult to obtain highly reproducible measurements. Several factors account for this, one of which is uncertainties in lesion identification, particularly very small white matter abnormalities. This paper aims to ascertain the significance of very small white matter abnormalities in the measurement of lesion load in multiple sclerosis.

Methods—All visible lesion areas identified by an experienced observer on proton density weighted spin echo brain MRI with 5 mm thick slices were measured by using a contouring technique in 15 patients with secondary progressive multiple sclerosis (SPMS) and 13 with relapsing remitting multiple sclerosis (RRMS). The size distribution of these lesions was analysed.

Results—80% of the number of the lesions were smaller than 80 mm². Lesions that were smaller than 10 mm² (equivalent diameter <3.5 mm) made up nearly 20% of all lesions; their relative contribution to the total lesion load varied from 0.0–5.7% (mean=1.1%, median=0.65%) in individual patients, and was larger when the total lesion load was smaller (r = –0.65, P<0.001). Median lesion size was significantly smaller in the SPMS group than the RRMS group.

Conclusions—The results suggest that it is prudent to identify and measure small lesions in evaluating treatment effects, and that measures are undertaken (for example, using thinner slices such as 3 mm) to improve their detection.

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Keywords: magnetic resonance imaging; multiple sclerosis; lesion volume

Quantitative measurement of lesion load on T2 weighted brain MRI in multiple sclerosis is a widely used marker of disease progression in treatment trials. However, it has been difficult to measure lesion load with a high degree of reproducibility. The coefficient of variation of measurement of lesion load reported in the literature ranges from 2%–34%. This high variability has multiple causes including differences in measurement techniques, image quality, slice thickness, scanner and rater performances, and lesion identification strategy.

At present, no gold standard exists for lesion identification and delineation. The consensus review of experienced neuroradiologists has been suggested as a best available “silver” standard, but inconsistency exists, even in the decisions of one radiologist made on different occasions. One particular difficulty is the lack of consensus on whether very small white matter abnormalities on MRI are significant and should be included as lesions for lesion volume measurement. Throughout this report we use the term small lesion to refer to white matter lesions in multiple sclerosis, seen on MRI, that are no larger than 3.5 mm in diameter. We have surveyed a data base of multiple sclerosis lesions to describe the distribution of lesion sizes to elucidate whether small lesions should be included and to what extent they influence overall lesion load measurement.

Materials

Patients

Twenty eight patients with clinically definite multiple sclerosis were studied. The patients had all been recruited into a double blind, placebo controlled trial of anti-CD4 antibody; full details of the criteria for entry to this study are published elsewhere. Fifteen of them had secondary progressive multiple sclerosis (SPMS) and 13 relapsing remitting multiple sclerosis (RRMS). Table 1 shows their clinical data.

MRI

Conventional dual spin echo axial proton density and T2 weighted MRI images were acquired for all patients on a GE Signa 1.5T scanner, using a birdcage head coil. The imaging parameters were: SE 2000/34/90, 5 mm thick contiguous interleaved slices, 256x256 matrix, 24 cm field of view, 1 excitation. The total number of slices was 28 for each echo. The scans were corrected for non-uniformity of the coil before being analysed.

Analysis

The lesions were identified and then segmented on the proton density weighted scans—under the supervision of a radiologist (MG-C)—by a neurologist who had two years of experience in the identification of white matter lesions.
Table 1  Patient information

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Sex (F:M)</th>
<th>Median EDSS</th>
<th>Mean disease duration (y)</th>
<th>Mean age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS</td>
<td>8:5</td>
<td>3.5 (2.0 - 6.0)</td>
<td>6.9 (1 - 22)</td>
<td>35.5 (26 - 47)</td>
</tr>
<tr>
<td>SPMS</td>
<td>7:8</td>
<td>6.0 (3.5 - 8.0)</td>
<td>10.3 (2 - 29)</td>
<td>40.5 (30 - 53)</td>
</tr>
</tbody>
</table>

RRMS=Relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis; EDSS=expanded disability status scale.

Values in parentheses are range.

Table 2  Results of analysis

<table>
<thead>
<tr>
<th>Measurement</th>
<th>RRMS</th>
<th>SPMS</th>
<th>Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lesion volume (ml)</td>
<td>35.7 (2.1 - 116.0)</td>
<td>42.4 (4.2 - 151.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Median lesion size (mm²)</td>
<td>40.9 (9.7 - 1011.0)</td>
<td>32.5 (1.8 - 3549.9)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Median No of lesions</td>
<td>75 (15 - 227)</td>
<td>96 (25 - 242)</td>
<td>NS</td>
</tr>
<tr>
<td>†SLV/TLV (%)</td>
<td>1.0 (0.0 - 4.7)</td>
<td>1.3 (0.0 - 5.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Significance inferred from Mann-Whitney rank sum test.
†SLV/TLV = small lesion volume × 100 / total lesion volume.
Results are given as mean (range).

Discussion and conclusions

Our evaluation of lesion size was based on the areas of the regions delineated on a slice by slice basis. This practice tends to bias towards the smaller lesion areas, as a confluent biological lesion going through several slices is treated as several smaller lesion regions. This may partly explain why the distribution of the number of lesions was skewed towards smaller sizes. However, as most of the lesion quantification methods used currently are based on region identification on individual slices on two dimensional images, we think that this approach is relevant.

Our findings suggest that small lesions should not be ignored in measurement of lesion volume. They can be quantitatively...
important, especially in patients with small total lesion loads. A subgroup of patients with multiple sclerosis in whom small lesions are especially prominent are those with primary progressive disease. It follows that quantification of small lesions in this subgroup should always be attempted. There may also be a case for considering patients with small, moderate, and large lesion loads separately.

The current study applies to 5 mm thick slices. Recent work on 3 mm thick slices found an 8% increase in total lesion load which is likely to reflect a contribution from small lesions. The increasing use of thinner slices for clinical trials is likely to result in identification of additional small lesions with important effects on measured lesion load; in the near future sequences such as three dimensional fast spin echo should provide isotropic resolution.

In the SPMS group a slightly higher proportion of the total lesion load was made up by small lesions and the median lesion size was significantly smaller compared with the RRMS group (table 2). Patients with SPMS also exhibited a different pattern of small lesion load contribution in relation to total lesion load from that of RRMS, as shown graphically in fig 3. Small lesions should be investigated more fully to ascertain whether their number and proportion are related to the clinical evolution of the disease. It is not inconceivable, for example, that the accumulation of mainly small lesions, none of which alone is sufficient to cause an acute relapse, might result in a slowly progressive increase in clinical disability. Future prospective studies are needed to consider this question.

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