Infratentorial Lesions Predict Long-term Disability in Patients With Initial Findings Suggestive of Multiple Sclerosis

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Background: The number and volume of abnormalities on baseline brain magnetic resonance images in patients with initial findings suggestive of multiple sclerosis are known to predict outcome in terms of disability. However, no long-term data exist on specific locations or types of lesions.

Objective: To assess the long-term predictive value of baseline magnetic resonance imaging parameters, including location of lesions and gadolinium-enhancing and hypointense lesions in patients with initial findings suggestive of multiple sclerosis for the occurrence of clinically relevant disability as defined by an Expanded Disability Status Scale score of 3.

Patients: After a median follow-up period of 8.7 years, the medical records of 42 patients were reviewed and assessed for time until patients received an Expanded Disability Status Scale score of 3. Magnetic resonance imaging parameters were dichotomized according to maximum accuracy and then used to calculate hazard ratios using the Cox model for proportional hazard ratios.

Results: Conversion to clinically definite multiple sclerosis was observed in 26 patients (62%), of whom 14 (54%) progressed to an Expanded Disability Status Scale score of 3. Two or more infratentorial lesions best predicted long-term disability (hazard ratio, 6.3). Gadolinium-enhancing and hypointense T1-weighted lesions did not show prognostic value.

Conclusion: Infratentorial lesions are related to long-term prognosis for patients with initial findings suggestive of multiple sclerosis and thus may help to identify patients at high risk for earlier occurrence of clinically relevant disability.

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INITIAL FINDINGS IN PATIENTS WHO eventually develop multiple sclerosis (MS) usually indicate a clinically isolated syndrome, although multisymptomatic onset does occur in a significant subset of patients. For these patients, there are 2 major concerns: the risk of development of clinically definite (CD) MS, and the prognosis with regard to disability if CDMS develops. Therefore, it would be desirable to have a model that estimates the risk of developing MS and accompanying disability, especially now that there is evidence that some patients will benefit from treatment in this early phase of the disease.

Several studies have shown the value of magnetic resonance imaging (MRI) in predicting the development of CDMS. Long-term follow-up studies demonstrate a conversion rate to CDMS of 35% to 80%. With the use of MRI, there is significant diagnostic gain. At their initial examination, most patients already have multiple white matter lesions on T2-weighted MRIs of the brain. The sensitivity, specificity, and accuracy differ between the proposed criteria.

However, the prediction of long-term disability is far more uncertain. Several studies described the significant relationship between lesion load at baseline and the Expanded Disability Status Scale (EDSS) score at 5 years' follow-up, which was also found after 14 years of follow-up. Morrisey et al7 and O’Riordan et al13 reported on the 5- and 10-year follow-up results in patients who were initially found to have optic neuritis, brainstem syndrome, or incomplete spinal cord syndrome. After 5 years, 20% had received an EDSS score greater than or equal to 3, whereas after 10 years, 30% showed progression to an EDSS score greater than 3. The type of initial symptoms seems to be important in this context: patients initially exhibiting optic neuritis are reported to have a low risk of reaching an EDSS score of 3 after a follow-up of 5 (4%) or even 15 (10%) years. The outcome of patients initially exhibit-
Table 1. Conversion to CDMS and Progression to an EDSS Score of 3 as Classified by Initial Findings

<table>
<thead>
<tr>
<th>Initial Findings</th>
<th>No. of Patients</th>
<th>CDMS</th>
<th>EDSS≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic neuritis</td>
<td>18</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Brainstem/cerebellar syndrome</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Spinal cord syndrome</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Brain syndrome</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Multisymptomatic</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>26</td>
<td>14</td>
</tr>
</tbody>
</table>

Abbreviations: CDMS, clinically definite MS (according to the Poser criteria); EDSS, Expanded Disability Status Scale.

*Data are given as number (percentage) of patients unless otherwise indicated.

ing a spinal cord syndrome appears to be worse: 20% of these patients reach an EDSS score greater than or equal to 3 within 3.5 years.9

Not only the presence or absence of lesions but also the location of lesions might be predictive of long-term disability. The presence of lesions in the infratentorial region on the baseline scan has been reported to correlate with EDSS score at follow-up12 and is likely one of the major predictive factors. In the studies mentioned so far, the predictive value of T1-weighted MRI parameters, such as gadolinium-enhancing and hypointense lesions for long-term disability has not been studied, and the location of the lesions on T2-weighted images was only scored as supratentorial or infratentorial.

In this study, we present the long-term follow-up results in a group of patients with a first episode of neurologic dysfunction suggestive of MS. To determine the prognostic value of baseline brain MRI findings in predicting the development of disability (EDSS score ≥3), we tested several MRI criteria, including gadolinium-enhancing and hypointense lesions on T1-weighted images and location of the lesions on T2-weighted images.

METHODS

PATIENTS

Forty-two patients (25 female, 17 male; female-male ratio, 1.5) with a first episode of neurologic dysfunction suggestive of MS were included. At initial examination, the mean age was 31.8 years (range, 12-52 years). Eighteen patients had optic neuritis, 6 patients had a brainstem or cerebellar syndrome, 6 patients had a brain syndrome (hemisensory and/or hemisensory syndrome), 4 patients had a spinal cord syndrome, and 8 patients were multisymptomatic. All patients were referred by neurologists and ophthalmologists before November 1992. The patients are part of a larger cohort (n = 39), from which findings have been reported previously.13,16 These previous studies described 10 patients in whom a diagnosis other than MS was ultimately made and 7 patients who were lost to follow-up. In the present study, medical records of the remaining 42 cases were reviewed by a single neurologist (C.H.P.) who was unaware of any MRI results. The following clinical parameters were assessed: initial symptom(s), date of conversion to CDMS, and date at which EDSS scores of 3 and 6 were reached. The EDSS thresholds were chosen because they represent the first and second major meaningful milestones of disability. The diagnosis of CDMS was made according to the criteria of Poser et al.17

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging had been performed on a 0.6-T machine before November 1992. Axial T2- and T1-weighted spin-echo images (repetition time/echo time/number of signals acquired, 2753/60120/2 and 450/28/4, respectively) were obtained. Each series consisted of 19 sections with a section thickness of 5 mm (1.25-mm gap), covering the whole brain. The T1-weighted spin-echo series was performed 3 to 10 minutes after the administration of 0.1 mmol/kg of gadolinium pentetic acid.

The MRIs were analyzed by consensus during a single session in which 2 observers were blinded to the clinical findings (as described earlier16). The following items were scored: the total number of (hyperintense) T2-weighted lesions, T2-weighted lesions greater than 6 mm, and the number of frontal, parietal, temporal, occipital, infratentorial, basal ganglia/internal capsule, periventricular, (juxta)cortical, and callosal/subcallosal lesions seen on T2-weighted MRI. On T1-weighted MRI, the number of enhancing (total and large >6 mm) and hypointense lesions were scored.

STATISTICAL ANALYSIS

Based on the clinical data, patients were classified as having no or minimal disability (EDSS score <3) or clinically relevant disability (EDSS score ≥3). Using progression to an EDSS score of 3 as the outcome, the accuracy of different cutoff levels was calculated for each MRI criterion. Final dichotomization for each MRI criterion was based on maximum accuracy.

The data were analyzed using proportional hazards regression according to the Cox model (likelihood ratio χ² test). Progression to an EDSS score of 3 was used as the dependent variable, while the dichotomized MRI criteria were used as independent variables. Univariate analyses were performed for each of the MRI criteria, and all MRI criteria were then explored together in a forward stepwise regression analysis to find the strongest predictive model.

RESULTS

The median duration of follow-up was 8.7 years (interquartile range [IQR], 7.9-9.3 years). In 26 patients (62%), a second attack occurred, and the diagnosis of CDMS was made (Table 1). The female-male ratio was 1.5. Fourteen (54%) of 26 CDMS patients progressed to clinically significant disability as marked by an EDSS score greater than or equal to 3. The median time to reach an EDSS score greater than or equal to 3 was 6.4 years (IQR, 1.2-7.8 years). Only 5 patients (19%) reached an EDSS score greater than or equal to 6, which precluded the use of this parameter as an outcome variable for statistical analysis.

T2-weighted MRIs showed 1 or more lesions in 34 patients (81%). The median number of lesions was 6.5 (IQR, 2.0-28.3) (Table 2). Most lesions were seen in the frontal lobes (median, 2.5; IQR, 0-11.3) and periventricularly (median, 2.0; IQR, 0-10.5). Relatively low numbers of lesions were seen infratentorially (median, 0; IQR, 0-2.0) and in the basal ganglia or internal capsule (median, 0; IQR, 0-3.0). Strong internal correlations were found among the various MRI criteria on T2-weighted images (data not shown). Four of 5 patients who
reached an EDSS score of 6 had infratentorial lesions; 3 of these had at least 2 lesions (data not shown).

The number of infratentorial lesions and the total number of lesions was high in patients with spinal cord syndrome (median, 33.5 and 2.5, respectively) and low in patients with optic neuritis (median, 3.5 and 0, respectively). At follow-up, no significant relationship was found between the presence of 1 or more lesions on T2-weighted images and an EDSS score of 3 (not dichotomized for maximum accuracy), a hazard ratio of 2.4, and \( P = .4 \) (not tabulated). After dichotomizing according to maximum accuracy, a high hazard ratio (6.8) was found for the total number of T2-weighted lesions, with a cutoff level of at least 9 lesions (Table 3). All dichotomized MRI criteria regarding location were significantly related to progression to an EDSS score of 3, with hazard ratios varying between 3.1 and 7.2. We did not find the predictive value of lesions by not only counting them, but also taking the location into account. This resulted in a significant correlation of the infratentorial lesion volume at baseline and EDSS score at 10 years. Our results confirm and extend these findings: in our final model only, infratentorial lesions are included as predictors of long-term disability. The other parameters, despite their good performance when tested in isolation, do not add independent information.

Finally, we performed forward stepwise proportional hazards regression. Using the time to reach an EDSS score of 3 as the dependent variable revealed that the presence of at least 2 infratentorial lesions was the best predictor (likelihood ratio \( \chi^2 \) test, 11.27; \( P = .001 \)). Adding more criteria did not result in significant improvement of the model, possibly owing to strong correlations between evaluated MRI criteria. Patients with at least 2 infratentorial lesions had a worse outcome at follow-up as measured by the percentage of patients who showed progression to an EDSS score of 3 (Figure).
There are at least 2 possible explanations for the observed dominance of infratentorial lesions in predicting the development of disability. First, damage to structures in the infratentorial compartment is likely to have an important effect on clinical disability, as has been emphasized before.22 Second, there is a close relationship between the spinal cord and the infratentorial compartment. The presence of infratentorial lesions may be an indicator for spinal cord disease, and the latter is known to correlate well with disability.23-26

Even though the presence of gadolinium-enhancing lesions is probably one of the best predictive MRI parameters for the development of CDMS,13,16,18,27 the relationship between gadolinium enhancement and the development of long-term disability is less clear. In a meta-

analysis by Kappos et al,28 both the baseline and monthly rates of gadolinium-enhanced MRI in MS patients were not predictive for the change in EDSS score in the following 1 or 2 years. These authors concluded that the presence of gadolinium-enhancing lesions is not a good predictor of long-term disability in patients with relapsing-remitting and secondary progressive MS. Our data confirm that the predictive value of gadolinium enhancement in patients at their first disease manifestation with respect to future disability is also limited. Despite our search for optimal cutoff levels, none of the T1-weighted MRI parameters was related to the development of disability.

There are several limitations to our study. Based on the clinical data available for follow-up, we were not confident to decide on the exact moment of conversion of relapsing-remitting to secondary progressive MS for many patients, and therefore, we were unable to include this parameter in our analysis. In addition, MRI scans were performed many years before on a 0.6-T machine, and the results perhaps cannot be compared directly with results from high-resolution scanning protocols using 1.0- or 1.5-T machines. Owing to technical problems regarding the storage of the electronic MRI data, it also was not possible to obtain lesion loads and incorporate these quan-

Table 3. Predictive Value of Dichotomized MRI Criteria for Progression to an EDSS Score of 3*

<table>
<thead>
<tr>
<th>MRI Criteria</th>
<th>Cutoff Value</th>
<th>Prevalence (n)</th>
<th>LR χ²</th>
<th>P Value</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-weighted images</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of lesions</td>
<td>9</td>
<td>20</td>
<td>9.21</td>
<td>.002</td>
<td>6.8</td>
</tr>
<tr>
<td>Periventricular lesions</td>
<td>3</td>
<td>20</td>
<td>9.81</td>
<td>.002</td>
<td>7.2</td>
</tr>
<tr>
<td>Callosal lesions</td>
<td>2</td>
<td>17</td>
<td>9.79</td>
<td>.002</td>
<td>6.1</td>
</tr>
<tr>
<td>Frontal lesions</td>
<td>4</td>
<td>20</td>
<td>8.88</td>
<td>.003</td>
<td>6.6</td>
</tr>
<tr>
<td>Parietal lesions</td>
<td>2</td>
<td>20</td>
<td>5.82</td>
<td>.02</td>
<td>4.1</td>
</tr>
<tr>
<td>Occipital lesions</td>
<td>3</td>
<td>11</td>
<td>4.36</td>
<td>.04</td>
<td>3.1</td>
</tr>
<tr>
<td>Temporal lesions</td>
<td>2</td>
<td>18</td>
<td>7.71</td>
<td>.006</td>
<td>5.0</td>
</tr>
<tr>
<td>Infratentorial lesions</td>
<td>2</td>
<td>11</td>
<td>11.27</td>
<td>.001</td>
<td>6.3</td>
</tr>
<tr>
<td>Basal ganglia or internal capsule</td>
<td>1</td>
<td>10</td>
<td>5.82</td>
<td>.02</td>
<td>3.8</td>
</tr>
<tr>
<td>(Juxta) cortical lesions</td>
<td>2</td>
<td>12</td>
<td>5.86</td>
<td>.02</td>
<td>3.7</td>
</tr>
<tr>
<td>Lesions &gt;6 mm</td>
<td>2</td>
<td>16</td>
<td>8.37</td>
<td>.004</td>
<td>5.0</td>
</tr>
<tr>
<td>T1-weighted lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypointense lesions</td>
<td>2</td>
<td>4</td>
<td>0.15</td>
<td>.69</td>
<td>1.4</td>
</tr>
<tr>
<td>Gadolinium enhancement</td>
<td>1</td>
<td>18</td>
<td>3.44</td>
<td>.07</td>
<td>2.8</td>
</tr>
<tr>
<td>Gadolinium-enhancing lesions &gt;6 mm</td>
<td>1</td>
<td>5</td>
<td>0.21</td>
<td>.66</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS, Expanded Disability Status Scale; LR, likelihood ratio; MRI, magnetic resonance imaging.

*Magnetic resonance imaging criteria were dichotomized according to maximum accuracy (cutoff value) and subsequently, hazard ratios were calculated using the Cox model for proportional hazard ratios.
titative data into our analyses. Furthermore, at the time of the first clinical examination, we did not routinely perform spinal cord imaging. Therefore, spinal cord abnormalities, potentially of great importance concerning disability development, could not be taken into account. The duration of follow-up in this study was such that the proportion of patients who reached an EDSS score of 6 was low, thereby preventing analysis of parameters predictive of more severe disability, although it may be speculated that there will be similarities with parameters correlated with moderate disability.

In conclusion, we found that several MRI criteria derived from baseline T2-weighted images were strongly related to progression to an EDSS score of 3 at follow-up. The presence of at least 2 infratentorial lesions was found to be the strongest predictor of progression to an EDSS score of 3. We did not find any prognostic value of MRI criteria derived from T1-weighted images, such as gadolinium-enhancing lesions and hypointense lesions for progression to an EDSS score of 3. Longer follow-up is needed to determine the predictive value of these criteria for more severe disability.

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REFERENCES