Specificity of Barkhof Criteria in Predicting Conversion to Multiple Sclerosis When Applied to Clinically Isolated Brainstem Syndromes

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Background: Barkhof criteria have been adopted to demonstrate dissemination in space in the new multiple sclerosis diagnostic criteria because of their high specificity for predicting conversion to multiple sclerosis. One of the 4 Barkhof criteria is the presence of an infratentorial lesion. In clinically isolated syndromes (CIS) of the brainstem (CISB), the infratentorial criterion does not demonstrate dissemination in space, raising the possibility that the criteria may be less specific in CISB, as compared with specificity in other CIS, in which all 4 criteria demonstrate dissemination in space.

Objective: To compare the validity indices of Barkhof criteria in CISB with those in other CIS.

Design: Inception cohort with median follow-up of 34 months for CISB and 40 months for other CIS.

Setting: Institutional ambulatory referral center.

Patients: A sample of 51 patients with CISB and 102 patients with other CIS (46 with myelitis and 56 with optic neuritis) was analyzed. Barkhof criteria, with a cutoff of 3 of 4, were applied to magnetic resonance imaging performed at baseline. Four combinations each containing 3 parameters were also applied, with a cutoff of 2 of 3.

Main Outcome Measure: Specificity of unmodified Barkhof criteria and of the 4 combinations to predict conversion to clinically definite multiple sclerosis.

Results: The specificity of the criteria in CISB was 61% against 73% in other CIS. The combinations that retained the infratentorial lesion parameter had lower specificities in the CISB group; in analysis of the group with other CIS, no such differences were found.

Conclusion: The infratentorial lesion criterion is responsible for the lower specificity of Barkhof criteria in CISB.

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Patients were recruited prospectively at our unit (Unidad de Neuroimmunología Clínica, Hospital Universitario Vall d’Hebron, Barcelona, Spain) from January 1995 through March 2001 and are part of the population with CIS previously described. Inclusion criteria were as follows: patients with an episode of brainstem, optic nerve, or spinal cord clinical dysfunction suggestive of inflammatory demyelination; patients aged 14 through 50 years; follow-up of 12 months or more; and clinical assessment within 3 months after symptom onset. Exclusion criteria were other possible diagnoses not adequately excluded and patients lost to follow-up.

FOLLOW-UP AND CLINICAL ASSESSMENT

Patients were asked on the first and all follow-up visits (every 3 to 6 months) about previous history of neurological disturbances. Conversion to MS was defined as the occurrence of a new clinical episode at least 1 month after remission of the initial event. A clinical attack was defined, as in the Poser criteria, as the occurrence of a symptom or symptoms of neurological dysfunction lasting more than 24 hours.9

MRI ASSESSMENT

The MRI was performed with either a 1.0-T or 1.5-T imager with a standard head coil and included the following pulse sequences: transverse proton density–weighted and T2-weighted conventional spin-echo (repetition time, 2200 milliseconds; echo time, 20-90 milliseconds; 1 signal acquired) or fast spin-echo (repetition time, 3000 milliseconds; echo time, 14-89 milliseconds; 2 signals acquired) and T1-weighted spin-echo (repetition time, 600 milliseconds; echo time, 15 milliseconds; 2 signals acquired). This last sequence was repeated after injection of 0.1 mmol of gadopentetate dimeglumine per kilogram of body weight, with an imaging delay of 5 minutes. We used a section thickness of 5 mm, a pixel size of approximately 1 × 1 mm, and an interleaved imaging mode with an intersection gap of 1.5 mm. Additional sequences, such as sagittal T2-weighted fast spin-echo (repetition time, 3550-5000 milliseconds; echo time, 90 milliseconds; 2 signals acquired) or transverse T2-weighted fast fluid-attenuated inversion-recovery (repetition time, 9000 milliseconds; echo time, 110-150 milliseconds; inversion time, 2200-2500 milliseconds; 11 signals acquired) were also performed in most patients.

One neuroradiologist (A.R.) who had expertise in MS and was blinded to all clinical details recorded the number and site of any abnormalities. The 4-parameter model proposed by Barkhof et al10 was then applied to each MRI study and was considered to be fulfilled when 3 of 4 of the dichotomized parameters were met. To investigate the specific performance of each criterion, we analyzed 4 subsets of criteria, each including 3 parameters, and set the positivity at 2 of 3.

STATISTICAL ANALYSIS

Statistical analysis was performed with a microcomputer version of the Statistical Package for Social Sciences (SPSS Inc, Chicago, Ill). To study the association between variables, we used the χ2 test. Statistical significance was set at P<.05 (2-tailed). The value of Barkhof criteria with regard to clinical follow-up was expressed as sensitivity, specificity, and accuracy. Accuracy was defined as follows: accuracy = (true-positive findings + true-negative findings) / (true-positive findings + true-negative findings + false-negative findings + false-positive findings). True positivity was defined as fulfilling Barkhof criteria and conversion to MS. False positivity was defined as fulfilling the criteria but not converting to MS, true negativity as not fulfilling Barkhof criteria and not converting to MS, and false negativity as not fulfilling the criteria but converting to MS.

RESULTS

Fifty-one patients with CISB, 46 with myelitis, and 56 with optic neuritis were included. Demographic and clinical variables are presented in Table 1. Eighteen (35%) of 51 patients in the CISB group and 23 (22%) of 102 patients in the myelitis and optic neuritis group had a second neurological episode suggestive of inflammatory demyelination in median follow-up periods of 34 and 40 months, respectively, thus converting to clinically definite MS. The conversion data per group were as follows: 13 (28%) of 46 in the myelitis group and 10 (18%) of 56 in the optic neuritis group.

Fulfilling the Barkhof criteria was associated with a high risk of conversion in CISB (P=.02) and in other CIS (P=.02). Validity indices of the Barkhof criteria in CISB, myelitis, and optic neuritis are shown in Table 2. We analyzed the fulfilling of 4 subsets, each including only 3 parameters, with the positivity set to 2 of 3. The subsets that retained the infratentorial lesion parameter had lower specificities in the CISB group; the subset not including the infratentorial lesion parameter showed the same values as when 4 parameters were used (Table 3).
In analysis of the group with myelitis and optic neuritis, no such differences were found, and all 4 subsets of Barkhof criteria performed similarly.

**Table 3. Validity Indices for Modified Subsets of Barkhof Criteria in CISB and Other CIS**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>CISSC/CISON</th>
<th>CISB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barkhof criteria (3 of 4)</td>
<td>73</td>
<td>61</td>
</tr>
<tr>
<td>Except gadolinium-enhancing or more than 9 lesions criterion (2 of 3)</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Except 3 periventricular lesions criterion (2 of 3)</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>Except juxtacortical lesions criterion (2 of 3)</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Except infratentorial lesions criterion (2 of 3)</td>
<td>66</td>
<td>64</td>
</tr>
</tbody>
</table>

Abbreviations: CIS, clinically isolated syndromes; CISB, CIS of the brainstem; CISON, CIS of the optic nerve; CISSC, CIS of the spinal cord.

*Data are given as percentages.
†Accuracy = (true-positive findings + true-negative findings)/(true-positive findings + true-negative findings + false-positive findings + false-negative findings).

The Barkhof criteria are the most specific MRI criteria available for assessing the risk of conversion to MS after CIS and have been incorporated into the new MS diagnostic criteria. However, they were assessed initially for mixed groups of CIS, and little is known about their performance in CISB. This lack is particularly relevant because many patients with CISB have an infratentorial lesion, which in this situation will not provide evidence of dissemination in space. As an example, in a patient with CISB in whom the cranial MRI study shows a gadolinium-enhancing brainstem lesion, an additional juxtacortical lesion is enough to demonstrate dissemination in space; a patient with optic neuritis attains 3 of 4 parameters less often.

The present study results show that the specificity for the Barkhof criteria in CISB, although higher than that of Paty et al or Fazekas et al, is less (61%) than that found in the cohort of other CIS (73%). The present data provide further evidence that the Barkhof criteria are less specific in CISB when compared with specificity in other CIS. The fact that this reduced specificity relates to the criterion specifying the presence of an infratentorial lesion is supported by examining subsets of Barkhof criteria with only 3 parameters and assuming as positive those patients fulfilling 2 of 3 criteria. Those subsets including the infratentorial lesion parameter were the least specific. No change in specificity was found for the cohort of other CIS; this value remained constant across all 4 subsets. Although longer follow-up periods than that of the present study (median of 3 years) could alter the present results, the focus here is on early conversion.

In summary, the Barkhof MRI criteria are not as specific in predicting conversion to MS in patients with CISB as when they are applied to other CIS, which is mainly because of the presence of the infratentorial lesion parameter. It might be instructive to assess the performance of modified Barkhof criteria in CISB, in which the infratentorial lesion parameter could be substituted by another criterion, such as the presence of callosal or subcallosal lesions.

**REFERENCES**