Association Between Clinical Conversion to Multiple Sclerosis in Radiologically Isolated Syndrome and Magnetic Resonance Imaging, Cerebrospinal Fluid, and Visual Evoked Potential

Follow-up of 70 Patients

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Background: Subclinical demyelinating lesions may occur in the brains of asymptomatic individuals.

Objective: To describe the clinical and magnetic resonance imaging (MRI) follow-up of patients with subclinical demyelinating lesions that fulfill the Barkhof/Tintoreé criteria.

Design: Prospective study.

Setting: University-affiliated teaching hospitals.

Patients: Fifty-three women and 17 men with subclinical demyelinating lesions (mean age, 35.63 years).

Main Outcome Measures: Cerebrospinal fluid, MRI, and visual evoked potential measurements.

Methods: All patients underwent their first brain MRI for various medical problems that were not suggestive of multiple sclerosis (MS). The patients' physicians proposed that they undergo paraclinical studies (blood, cerebrospinal fluid, and visual evoked potential analysis) and follow-up with MRI.

Results: Twenty-three patients (33%) had clinical conversion: 6 to optic neuritis, 6 to myelitis, 5 to brainstem symptoms, 4 to sensitive symptoms, 1 to cerebellar symptoms, and 1 to cognitive deterioration. The mean time between the first brain MRI and the first clinically isolated syndrome was 2.3 years (range, 0.8-5.0 years). Twelve patients had been treated with immunomodulators after a clinically isolated syndrome. Examination of pejorative markers for clinical conversion showed that sex, number of T2 lesions, presence of oligoclonal bands, and IgG index were not statistically different in patients with MS determined by MRI compared with clinically definite MS. Visual evoked potential abnormalities, young age, and gadolinium enhancement on follow-up MRI were more frequent in clinically definite MS than in MS determined by MRI.

Conclusions: In this cohort, we determined the rate of clinical conversion (33%) during a mean follow-up of 5.2 years. To our knowledge, this is the first clinically isolated syndrome cohort with preclinical follow-up. Early treatment of these patients with MS determined by MRI should be discussed.

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Few case reports have been published on patients with asymptomatic demyelinating lesions with suspicion and final diagnosis of relapsing-remitting or primary progressive multiple sclerosis (MS). We recently reported on a descriptive retrospective study of the clinical characteristics and 5-year magnetic resonance imaging (MRI) follow-up of patients with subclinical demyelinating lesions that fulfill the criteria of Barkhof et al. and Tintoreé et al. The patients' neurological examination results were normal, which shows the importance of the demonstration of dissemination of the disease in time and space during the preclinical phase. We report herein on a new prospective descriptive study concerning 70 patients with subclinical MS (radiologically isolated syndrome [RIS]) and describe the predictive clinical, imaging, and electrophysiologic factors in diagnosing a clinically isolated syndrome (CIS).

Methods: From 2000 to 2008, a total of 7 patients who presented with brain asymptomatic T2-
BIOLOGICAL SCREENING

All patients initially had normal neurological and biological analysis results. All patients underwent biological and immunological tests, including a complete blood cell count and measurements of erythrocyte sedimentation rate, serum cryoglobulins, total serum gamma globulins, serum protein immunoelectrophoresis, C-reactive protein, complement factors, antinuclear antibodies, antinative DNA, antiphospholipid/anticardiolipin antibodies, rheumatoid factor, antiprothrombinase, human immunodeficiency virus, herpes simplex virus, varicella-zoster virus, hepatitis C and B, cytomegalovirus, and Epstein-Barr virus serology.

All patients underwent CSF analysis with cell count and a protein level and oligoclonal band evaluation by isoelectrofocusing methods. Detection of oligoclonal bands was considered positive if more than 1 band that was not detected in the serum was present in CSF.

STATISTICAL ANALYSIS

Intergroup comparison was performed with the Fisher exact test for categorical variables and with the Wilcoxon test for quantitative variables. All tests were 2-tailed and P < .05 was considered statistically significant. Comparison between relative frequencies was done using the χ² distribution. Survival analysis was used to assess time-dependent variables. The end point was the time from the first MRI to the CIS and was analyzed using Kaplan-Meier estimates. Survival curves were compared using the log-rank test.

RESULTS

Seventy patients were identified: 53 women and 17 men with a mean age of 35.63 years (range, 16-48 years; mean age: men, 35.3 years; women, 35.7 years) (Table 1). Nine patients had a relevant family history (5 with MS and 4 with migraine). Twenty-five patients had a medical background: migraine (n = 12), depression (n = 7), endocrinologic disorders (n = 4), atopic eczema (n = 2), and breast cancer (n = 1). The first brain MRI was usually ordered by the general practitioner for various medical events, including headache (n = 24), migraine with (n = 4) or without (n = 10) aura, craniofacial trauma (n = 2), depression (n = 7), tinnitus (n = 7), radiculalgia (n = 5), endocrinopathies (n = 3), childhood epilepsy (n = 2), cognitive complaint (n = 1), anosmia (n = 1), and dystonia (n = 1); 3 patients had volunteered to undergo MRI. None of these complaints were related to suspicion of a demyelinating event. Even if depression and radiculalgia rarely precede MS, it cannot be definitively disregarded as a CIS. The mean follow-up time for the whole cohort was 5.2 years (range, 3-6.4 years). The mean time between the

### Table 1. Patient Characteristics After Paraclinical Examination

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CIS (n = 23)</th>
<th>MS on MRI (n = 47)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First MRI</td>
<td>15</td>
<td>2</td>
<td>.05</td>
</tr>
<tr>
<td>Second MRI</td>
<td>11</td>
<td>8</td>
<td>.02</td>
</tr>
<tr>
<td>Both MRIs</td>
<td>9 (39)</td>
<td>3 (6.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Infratentorial lesions</td>
<td>8 (34.8)</td>
<td>37 (78.7)</td>
<td>.048</td>
</tr>
<tr>
<td>Abnormal VEP</td>
<td>20 (87)</td>
<td>25 (53)</td>
<td>.02</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>12 (52.1)</td>
<td>18 (38.2)</td>
<td>.27</td>
</tr>
<tr>
<td>Increased IgG index</td>
<td>12 (52.1)</td>
<td>16 (34)</td>
<td>.14</td>
</tr>
<tr>
<td>Oligoclonal bands and increased IgG index</td>
<td>11 (47.8)</td>
<td>12 (25.5)</td>
<td>.06</td>
</tr>
<tr>
<td>≥9 T2-hyperintense lesions and gadolinium enhancement</td>
<td>11 (47.8)</td>
<td>9 (19.2)</td>
<td>.02</td>
</tr>
<tr>
<td>≥9 T2-hyperintense lesions, gadolinium enhancement, and abnormal VEP</td>
<td>10 (43.5)</td>
<td>2 (4.2)</td>
<td>.04</td>
</tr>
<tr>
<td>≥9 T2-hyperintense lesions, gadolinium enhancement, oligoclonal bands, and increased IgG index</td>
<td>7 (30.4)</td>
<td>2 (4.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Met all criteria</td>
<td>7 (30.4)</td>
<td>1 (2.1)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CIS, clinically isolated syndrome; MRI, magnetic resonance imaging; MS, multiple sclerosis; VEP, visual evoked potential.

a Only 1 patient who met all criteria had not yet presented with neurological symptoms.
first consultation and the first brain MRI was 5 months (range, 1-48 months). Seventeen patients had initial gadolinium enhancement, 58 had at least 9 T2-hyperintense lesions, and 45 had infratentorial lesions (Table 1). Cerebrospinal fluid analysis revealed a mean cell count of 3 cells/mm³ (range, 0-16 cells/mm³; with 28 patients having >4 cells/mm³). Thirty patients had oligoclonal bands and 28 had an increased IgG index. Forty-five patients had an abnormal asymptomatic VEP. For the 12 patients with fewer than 9 T2-hyperintense signals on brain MRI, CSF abnormalities were seen in 2 cases associated with an abnormal VEP. Among the 58 patients with at least 9 T2-hyperintense signals, 38 of 58 (65.5%) had an abnormal VEP and 48 of 58 (82.7%) had a positive CSF result. The mean time until the second brain MRI was 6 months (range, 3-30 months) (3-6 months in 34 patients, 6-12 months in 14 patients, 12-24 months in 21 patients, and 30 months in 1 patient). Sixty-four patients (91%) had dissemination in time, including 20 of 64 patients (37%) with new gadolinium enhancement and 47 with at least a new T2 lesion. Patients with dissemination in time were considered to have MS on MRI. During follow-up, 23 of 70 patients were found to have clinical conversion to the following conditions: optic neuritis (n=6), myelitis (n=6), brainstem (diplopia or internuclear ophthalmoplegia) symptoms (n=5), sensitive symptoms (paresthesias in lower or upper limbs) (n=4), cerebellar symptoms (n=1), and cognitive deterioration (n=1). No progressive form of MS was detected. No particular event (infection or vaccination) was found in the 3 months before the CIS. The mean time between the first brain MRI and CIS was 2.3 years (range, 0.8-5.0 years). Twelve patients had been treated with immunomodulators after the CIS: 8 with interferon and 4 with glatiramer acetate (4 patients after the second relapse). Of patients who had MS diagnosed according to McDonald criteria,3,10,11 4 had their first clinical event during the first year after the initial MRI, 6 patients had it during the second year, 11 had it during the third and fourth years, and 2 had it at 5 years (Figure 1). The mean age at development of a CIS was 34.2 years. Eight of 23 patients had 2 relapses, with a mean delay of 9 months. To date, the mean Expanded Disability Status Scale (EDSS) score for the 23 patients who had a CIS is 1.5 (range, 0-4), with a mean follow-up after the CIS of 2.1 years. Considering MRI criteria, we found that only gadolinium enhancement on MRI and infratentorial lesions were statistically significant for clinical conversion in a univariate analysis (P=.01) (Table 1). Associated MRI criteria (≥9 T2-hyperintense lesions and gadolinium enhancement) predicted CIS (P<.05). When comparing patients with initial symptoms that are unlikely to represent demyelinating events with those who had symptoms that possibly represented a CIS, only gadolinium enhancement was statistically significant (P=.005) (Table 2). The CSF criteria were only statistically significant when associated with 9 or more T2-hyperintense lesions on the first MRI on multivariate analysis (P=.02) (Figure 2). An abnormal VEP at presentation was a significant pejorative marker for developing CIS in a univariate analysis (P<.05) (Table 3).

Meeting MRI criteria for MS, added to CSF abnormalities alone or to a VEP abnormality, was associated with an increased risk of a CIS. Among the patients with CIS, 7 (30.4%) met all of the studied criteria before clinical conversion (Table 1) and only 1 (2.1%) patient in the nonconversion group met all of the criteria. The mean residual EDSS score of these patients with CIS was 2.8 (range, 1-6), which is worse than the whole CIS but not statistically significant.

The concept of preclinical MS is now recognized and is an exciting concept for neurologists. Case reports have already been published for first-degree relatives of patients with MS who are at particular risk, demonstrating 10% of subclinical demyelination in asymptomatic siblings in a particular population in Sardinia.12,13 We have already described a cohort of 30 pre-MS patients who presented with subclincal MS and had MS dissemination criteria in space on MRI.9 Twenty-six of the 70 patients (37%) of this new cohort had developed a CIS with a clinical expression corresponding to that reported in a review of a large database of patients with CIS, which found that 21% presented with optic neuritis, 46% presented

![Figure 1. Kaplan-Meier survival curve showing the risk of developing a clinically isolated syndrome (CIS). At 1 year, 92% of patients have not had a CIS. At 2 years, 82% of patients have not had a CIS. At 3 years, 59% of patients have not had a CIS.](http://archneur.jamanetwork.com/pdfaccess.ashx?url=/data/journals/neur/7761/)

![Table 2. Initial Symptoms Leading to Brain Magnetic Resonance Imaging](http://archneur.jamanetwork.com/pdfaccess.ashx?url=/data/journals/neur/7761/)
with long tract symptoms and signs, 10% presented with a brainstem syndrome, and 23% presented with multifocal abnormalities.14,15 This comparison allows us to conclude that our cohort is representative of potential pre-MS disease.

In the CIS literature, older age at onset and a higher number of MS attacks during the first 2 years of MS proved to be predictors of unfavorable prognosis.16 In our cohort, patients who presented with a CIS were younger than the mean age of the whole cohort with a relatively short preclinical phase. Patients with clinically definite MS are not as young as the patients with CIS published in the literature. This result could imply that demyelinating disease does not occur as early as reported.

To date, 8 of 23 patients had 2 or more relapses after a CIS. As already published for CIS cohorts, the first interattack interval had no influence on the evolution of the disability, in contrast to the first relapse, which had a short-term impact on prognosis. A recent study demonstrated that, among the patients with relapsing-remitting MS, the 2 variables that predict more rapid progression toward disability are an older age at onset of MS and incomplete recovery from the first relapse. In addition, multivariate analysis showed that female sex or a longer period between the first 2 attacks are not pertinent variables in predicting rapid progression toward disability.17 In our study, we did not find any differences by sex or initial symptom that could predict neurological conversion or relapse frequency.

Researchers have found that lesions on MRI of a CIS are strongly predictive of diagnosis and that the number of lesions is related to the time to relapse and subsequent disability.18,19 At 1 year of follow-up, 10% of our patients had a CIS. In other series of patients with a documented CIS, more than 3 times as many patients with a CIS were diagnosed with MS using the McDonald diagnostic criteria 1 year after symptom onset.20 Gadolinium enhancement and T2 lesions are prognostic factors in documented CIS.21 In a study of MRI examination of 68 patients with a CIS and clinical assessment after 1 year, contrast enhancing lesions at both points were the most predictive indices for developing MS. The relationship between the initial count of gadolinium-enhancing lesions and subsequent worsening in disability or impairment as measured by the EDSS score and relapse rate is less clear.22 Gadolinium enhancement does not seem to be a strong predictor of the development of cumulative impairment or disability, but the Barkhof/Tintore´ criteria at presentation and dissemination are statistically significant. Infratentorial lesions were frequent in our cohort and a univariate analysis showed that it was a prognostic factor for a CIS. It has been published that the infratentorial lesion criterion is responsible for the lower specificity of Barkhof/Tintore´ criteria in CISs involving the brainstem.23 The specificity of the criteria in these infratentorial CISs was 61%, compared with 73% in other CISs. Our results for patients with RISs are comparable.

Intrathecal immunoglobulin synthesis and oligoclonal bands are found in more than 90% of patients with MS. In our study, 72.8% of patients had at least 1 abnormal

Table 3. Prognostic Factors for Developing a Clinically Isolated Syndrome

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>No. of Patients by Presence or Absence of Prognostic Factor</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First MRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadolinium enhancement</td>
<td>17 33  .46</td>
<td></td>
</tr>
<tr>
<td>≥9 T2-hyperintense signals</td>
<td>58 12 .50</td>
<td></td>
</tr>
<tr>
<td>Infratentorial lesions</td>
<td>45 19  .47</td>
<td></td>
</tr>
<tr>
<td>Barkhof/Tintore´ criteria</td>
<td>56 14 .08</td>
<td></td>
</tr>
<tr>
<td><strong>Second MRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadolinium enhancement</td>
<td>20 50 .01</td>
<td></td>
</tr>
<tr>
<td>≥9 T2-hyperintense signals</td>
<td>63 7  .18</td>
<td></td>
</tr>
<tr>
<td>Infratentorial lesions</td>
<td>45 25  .57</td>
<td></td>
</tr>
<tr>
<td>Dissemination</td>
<td>64 6  .07</td>
<td></td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4 Cells/mm³</td>
<td>28 42  .61</td>
<td></td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>30 40  .69</td>
<td></td>
</tr>
<tr>
<td>Increased IgG index</td>
<td>28 42  .26</td>
<td></td>
</tr>
<tr>
<td>1 Abnormal result in CSF</td>
<td>51 19  .66</td>
<td></td>
</tr>
<tr>
<td><strong>VEP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>45 25  .04</td>
<td></td>
</tr>
<tr>
<td>1 Abnormal result in CSF and ≥9 T2-hyperintense lesions on first MRI</td>
<td>48 22  .02</td>
<td></td>
</tr>
<tr>
<td>Abnormal VEP and ≥9 T2-hyperintense lesions on first MRI</td>
<td>38 32  .12</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; VEP, visual evoked potential.
nal result on CSF analysis. Interestingly, using the univariate analysis, oligoclonal bands or an increased IgG index was not a predictive factor for a CIS. It was statistically significant only if associated with a high T2-hyperintense lesion load at presentation in accord with a recent study, which demonstrates that the presence of oligoclonal IgG bands plus 2 T2-hyperintense lesions accurately predicts CIS conversion to MS. Magnetic resonance imaging and CSF criteria have a high specificity but less sensitivity and accuracy. These results reinforce the role of CSF examination in MS diagnosis. Using the univariate analysis, the CSF characteristics (leukocyte count, IgG index, and oligoclonal bands) had no marked predictive value for developing clinically definite MS compared with MRI parameters.5

In our study, an abnormal VEP correlates with other well-known paraclinical markers of acute brain inflammation, such as a high number of MRI T2-hyperintense lesions, the presence of gadolinium-enhancing MRI lesions, total number of CSF cells, and intrathecal IgG synthesis. Logically, most of the patients with at least 9 T2-hyperintense lesions on MRI had abnormal VEPs. Our findings from this cohort seem to differ from the usual conclusions that show that the differentiating characteristics of patients with the earliest form of MS are predominantly afferent symptoms, less brain MRI dissemination, and more frequently a normal VEP but abnormal CSF findings with elevated CSF cells and positive oligoclonal bands.20

For patients with RIS without clinical events but with evidence of dissemination in time and space, discussion concerning therapeutic options aimed at reducing the risk of developing MS should point out that subclinical MS can evolve. Such discussion is not easy and some patients could insist on being treated.27 In CIS, early treatment seems to influence the relapse location.28 In our cohort, patients who experienced CIS did not have a pejorative evolution. To date, the mean EDSS score for patients who experienced CIS was 1.5, with a mean follow-up after the CIS of 2.7 years.34 This result fits with other described CIS cohorts, treated or not treated.29,30

It is not known if patients in the preclinical phase and with evidence of disease activity have to be treated. It is very important to apply confident MRI criteria and guidelines for guidance on the differential diagnosis process when MS on MRI is suspected. A recent study describes a cohort of 44 subjects with RIS; among the 30 subjects for whom there was clinical follow-up, 10 developed a CIS or clinically definite MS after a median of 5.4 years.31 Radiologic progression occurred in 59% of cases during a median of 2.7 years. In our series, patients with baseline MRI scans demonstrating gadolinium-enhancing lesions exhibited a substantial increased risk of developing new lesions. However, it is not known if the patients were at risk of developing a CIS. The Task Force on Differential Diagnosis in MS has proposed identifying patients without typical presentation suggestive of demyelinating disease but with an MRI suggestive of a type of CIS.32 In our study, 8 patients’ conditions were converted to definite MS after they had 2 clinical attacks; 15 patients presented with a CIS and fulfilled modified McDonald criteria for MS; 6 patients did not develop clinical symptoms or new MRI lesions; and 41 patients did not develop clinical symptoms, but developed dissemination in time and space according to modified McDonald MRI criteria. We think that if Barkhof/Tintoré criteria are fulfilled on initial brain MRI for a patient suspected of having RIS, paraclinical screening, clinical evaluation, and follow-up MRI should be proposed.

Given the current emphasis of starting MS treatment as soon as possible, the question of starting it before the clinical event is challenging. For some authors, patients showing dissemination on MRI without symptoms would not be considered to have MS.33 The burden of diagnosis and long-term treatment cannot be imposed on patients who might never show symptoms of the illness. Long-term disability will be assessed with extensive follow-up for patients who have RIS and compared with CIS cohorts. One day we may be able to identify patients with RIS who warrant immunomodulatory treatment, but to date, we are not allowed to prescribe it.

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REFERENCES


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