A Longitudinal Study of Callosal Atrophy and Interhemispheric Dysfunction in Relapsing-Remitting Multiple Sclerosis

J. Pelletier, MD, PhD; L. Suchet, MD; T. Witjas, MD; M. Habib, MD; C. R. G. Guttmann, MD, PhD; G. Salamon, MD; O. Lyon-Caen, MD; A. Ali Cherif, MD

Objectives: To determine if callosal atrophy and interhemispheric dysfunction can be detected in the early stages of relapsing-remitting multiple sclerosis (MS) and to evaluate their progression in relation to the disability and evolution of lesions seen on magnetic resonance imaging during a 5-year period.

Methods: We compared 30 patients who had clinically definite early-onset relapsing-remitting MS and mild disability with control subjects. Regional and segmental callosal size and extent of white matter abnormalities on magnetic resonance imaging, as well as performance on tasks exploring interhemispheric transfer of motor, auditory, and sensory information were assessed. Patients with MS were evaluated at baseline and after 5 years. Physical disability was determined at both times using the Expanded Disability Status Scale score.

Results: Patients with MS were seen with significant callosal atrophy and functional impairment of interhemispheric transfer at baseline that worsened during the 5-year study. A significant correlation was found between the magnitude of disability and the severity of morphological and functional callosal involvement at baseline. This association persisted at year 5. Baseline clinical characteristics such as age and prestudy relapse rate were unrelated to callosal size or interhemispheric performance. However, the number of baseline T2-weighted lesions was correlated with callosal involvement and this relation persisted at year 5.

Conclusion: Patients who had relapsing-remitting MS in the early stages of the disease and mild disability had significant callosal involvement that progressed over time. The relationship between disability, T2-weighted lesions load, and degree of morphological and functional callosal impairment confirm the potential value of using callosal dysfunction as a surrogate marker of disease progression in MS.

Arch Neurol. 2001;58:105-111
PATIENTS AND METHODS

PATIENTS

Of the 90 patients with MS who were initially examined and enrolled in our original study,32 30 were still available and were considered suitable for our 5-year follow-up study. Inclusion criteria were: (1) clinically definite RR MS as determined by the criteria of Poser et al32 with a clinically documented MS duration of less than 3 years at baseline, (2) no long-term treatment for MS during the follow-up period, (3) clinical remission at the time of evaluation, (4) no major signs of cerebellar, motor, or sensory involvement of the upper limbs at baseline examination, and (5) hemispheric white matter hyperintensities on T2-weighted MRI consistent with the diagnosis of MS32 at baseline MRI. All patients’ disabilities were scored using the EDSS30 at both times by the same evaluating neurologist (J.P.).

CONTROL SUBJECTS

Twenty-five sex-, age-, and handedness-matched normal subjects without known neurological disorders or history of alcoholism or other drug abuse were recruited as controls and underwent neuropsychological testing. This group had a mean age of 29 years (age range, 20–40 years). Normal callosal morphology was defined by a previous study of 53 healthy volunteers who had undergone the same MRI procedure as used for this study.31

NEUROPSYCHOLOGICAL TESTING

Interhemispheric transfer of auditory (verbal dichotic listening task), sensory (crossed tactile finger localization), and motor (finger-tapping task) information was evaluated in all patients and controls at baseline and 5 years later for the group with MS only. The detailed procedure has been previously described.22 Twenty-eight patients had normal brainstem auditory evoked potentials. For the remaining 2 patients, it was verified individually that abnormal brainstem auditory evoked potentials could not account for the asymmetry in dichotic listening performance. Data analyses were based on functional transfer (FT) indexes (mean difference in errors between the 2 ears for verbal dichotic listening task; mean difference in errors between intermanual and monomodal conditions for sensory transfer task, and mean ratio between monomodal and bimanual conditions for motor transfer task).22

MAGNETIC RESONANCE IMAGING

The design of this study was performed in 1991 and we used the same MRI unit (Magneton; Siemens, Erlangen, Germany) operating at a field strength of 1.5 T at baseline and at year 5. The image resolution was 0.89 mm in-plane for 5-mm-thick sections (acquisition matrix, 256 × 256 pixels; field of view, 23 cm) and imaging was done in the axial and sagittal planes. The axial section thickness was 5 mm and computed tomographic scans were performed on patients using a T2 sequence with a repetition time of 2700 milliseconds and an echo-delay time of 20 to 90 milliseconds. All patients were also evaluated by T1-weighted sagittal partial saturation images using a repetition time of 600 milliseconds and an echo-delay time of 20 milliseconds (slice thickness, 5 mm).

MRI ANALYSIS

Quantification of CC morphology was carried out from the T1-weighted midsagittal MRI. Global and segmental morphology of the CC was assessed with automated measurements based on a manual midsagittal outline of the CC. The midcallosal area was partitioned into the following 6 subregions: 3 anterior (A1, A2, and A3) and 3 posterior (P1, P2, and P3) regions.23 The extent of T2 white matter lesions was assessed on axial sections using a semiquantitative method with a 5-point grading scale (total lesion index).32 Regional distribution of lesions within and outside of the CC was analyzed for an anterior (A3+A2), middle (A1+P1), and posterior (P2+P3) region using the same 5-point scale. Each axial image was subdivided into these 3 regions by projecting the boundaries calculated on the midsagittal image (Figure). Magnetic resonance imaging scans were graded independently by 2 blinded physicians (L.S. and T.W.). Interrater agreement was high (0.87 for lesion grading; 0.96 for CC measurements).

STATISTICAL ANALYSIS

Analysis of variance (ANOVA) was performed to characterize the overall relationship between callosal functional performances and morphological measures on both data series (at baseline and at year 5). Multiple stepwise regression analysis was computed to assess the relationship between FT impairment, CC atrophy, and baseline and 5-year measures. Patients’ and controls’ FT scores, as well as global and segmental callosal morphology measures of patients with MS and controls were compared using the t test. Spearman rank correlation coefficients were calculated to characterize the relationship between clinical, functional, and MRI measures. The t tests were used to compare baseline and year 5 changes for callosal morphology and functional performances. All statistical analyses were performed on a Macintosh personal computer (Apple Computer Inc, Cupertino, Calif) using StatWorks (version 1.1, 1985; Macintosh Inc, Apple Computer Inc) and CLR ANOVA (1992; Middivision Software, Abacus Concept Inc, Berkeley, Calif) softwares.

the progression of cerebral atrophy.13 Another valuable method to evaluate axonal loss could be provided by studying callosal anatomy and interhemispheric function.

Autopsy and MRI studies indicate that atrophy of corpus callosum (CC) is a common finding in patients with MS.14-24 Demyelinating lesions of callosal or subcallosal areas found in most patients with MS could explain CC atrophy.17,20 However, some studies demonstrated dysfunction of interhemispheric transfer in patients with MS, particularly on verbal dichotic listening tasks showing a left-ear dichotic suppression.18,22,25-27 Functional impairment of interhemispheric transfer in MS has also been correlated to the degree of callosal atrophy and to the severity and diffusion of white matter changes identified by MRI.18,22,23 Moreover, it has been recently shown
that even in cases where high-resolution MRI had failed to demonstrate cerebral demyelination, interhemispheric dysfunction and, to a lesser degree, callosal atrophy may be present. This unexpected result could be interpreted as witnessing infraradiological involvement of callosal fibers that could be therefore viewed as an early marker of axonal and neuronal damage.

To determine the potential value of callosal atrophy and interhemispheric transfer impairment as a sensitive marker of MS progression, we conducted a 5-year prospective study in a group of patients with RR MS enrolled at the early stage of MS who had mild disability based on EDSS scores. The aims of this study were to (1) assess whether callosal atrophy and interhemispheric impairment could be detected in patients with RR MS early in the disease, (2) determine if functional and morphological callosal impairments progress during a 5-year period, (3) evaluate the potential relationship between functional and morphological callosal measures and disability, and (4) determine the influence of T2 lesions on callosal involvement as seen on MRI.

**RESULTS**

**BASELINE CHARACTERISTICS**

Demographic and clinical characteristics of the MS population are summarized in Table 1. As determined by the inclusion criteria, patients were at the early stage of MS (mean disease duration, 2.4 years) with a low EDSS score (mean EDSS score, 2.1).

**Functional Interhemispheric Transfer Assessment**

As previously reported, patients with MS were significantly impaired compared with controls for all modalities explored (left ear extinction, hands-tactile condition, and increased time in bimanual tapping [Table 2]).

**Callosal Morphology on MRI**

The comparison of mean callosal areas between the population with MS and the controls showed significant atrophy in the group with MS for global callosal area, as well as for all 6 subregions (P < .001) (Table 3). We found no significant effect or interaction of gender and hand preference on callosal area measurements in patients with MS.

**Correlations Between MRI and Neuropsychological Measures**

The global ANOVA performed on the baseline results showed a significant interaction between performance on FT tasks for all modalities explored and EDSS score (F = 4.25, P < .01). A significant interaction was also found.

---

**Table 1. Demographic and Clinical Characteristics of Population With Multiple Sclerosis (MS)***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Value (N = 30)</th>
<th>Year 5 Value (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>11/19</td>
<td>...</td>
</tr>
<tr>
<td>Age, mean (± SD), y</td>
<td>27 (± 6.3)</td>
<td>...</td>
</tr>
<tr>
<td>Handedness, R/L</td>
<td>28/2</td>
<td>...</td>
</tr>
<tr>
<td>Prestudy disease duration, y</td>
<td>2.4 (± 0.77)</td>
<td>...</td>
</tr>
<tr>
<td>EDSS score, mean (± SD), [range]</td>
<td>2.1 (± 1.03) [1-4]</td>
<td>4.6 (± 1.56) [2.5-7]</td>
</tr>
<tr>
<td>Clinical course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR MS, No. of patients</td>
<td>30</td>
<td>...</td>
</tr>
<tr>
<td>Prestudy annual relapse rate, mean No. (± SD)</td>
<td>1.3 (± 0.32)</td>
<td>...</td>
</tr>
<tr>
<td>Annual relapse rate during study, mean No. (± SD)</td>
<td>...</td>
<td>1.5 (± 0.43)</td>
</tr>
<tr>
<td>SP MS, No. (%) of patients</td>
<td>... 7 (20)</td>
<td>...</td>
</tr>
<tr>
<td>Abnormal BAEPs, No. (%) of patients</td>
<td>2 (7)</td>
<td>7 (20)</td>
</tr>
</tbody>
</table>

*Ellipsis indicates not applicable; EDSS, Expanded Disability Status Scale; RR, relapsing-remitting; SP secondary progressive; and BAEPs, brainstem auditory evoked potential (abnormality in one or both ears).

**Table 2. Performance of Patients With Multiple Sclerosis (MS) and Controls on Functional Tasks of Interhemispheric Transfer at Baseline and Year 5*"**

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Controls (n = 25)</th>
<th>Patients With MS (n = 30)</th>
<th>t/Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichotic listening†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.2 (1)</td>
<td>9.2 (5.1)</td>
<td>8.67</td>
</tr>
<tr>
<td>Year 5</td>
<td>... 12.2 (7.8)‡</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Sensory transfer§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.9 (0.8)</td>
<td>8.6 (4.6)</td>
<td>6.42</td>
</tr>
<tr>
<td>Year 5</td>
<td>... 13.9 (6.4)‡</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Motor transfer¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.36 (0.03)</td>
<td>0.45 (0.14)</td>
<td>4.45</td>
</tr>
<tr>
<td>Year 5</td>
<td>... 0.48 (0.17)‡</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

*Per t test all P values for each test were less than .001. All values are expressed as means (SDs) unless otherwise indicated. Ellipsis indicates not applicable.

†Mean difference in errors between the 2 ears (left ear vs right ear).
‡P < .05 (comparison of patients with MS between baseline and year 5).
¶Mean difference in errors between intermanual and monomodal conditions.
§Mean ratio of unimanual vs bimanual tapping time.
between CC morphology and EDSS score \( (F = 5.89, P < .001) \) and between T2 MRI lesion grading and EDSS score \( (F = 4.39, P < .01) \). The stepwise regression confirmed that the EDSS score was predominantly linked to dichotic listening \( (F = 10.625) \) and sensory transfer tests \( (F = 9.34) \) for interhemispheric transfer, to A3 and P3 areas for callosal morphology \( (F = 12.6) \), and to total index for MRI white matter lesions. A significant correlation was found between the magnitude of relative left ear impairment and all callosal measurements carried out (Table 4). Similarly, significant correlations were noted between severity of transfer impairment for tactile and motor tasks and callosal atrophy except for the splenium. As we previously reported, each FT was predominantly associated with atrophy of one part of the CC (anterior region for motor transfer, middle region for tactile localization task, and posterior region for dichotic listening task) (Table 4). Correlation between regional grading of T2 MRI white matter abnormalities and functional impairment of interhemispheric transfer tests demonstrated a global relation between the dichotic listening task score or the sensory transfer test score and each callosal measure \( (P < .01) \). In contrast, a preferential relationship between the motor transfer test and lesions localized in the middle and anterior regions was found (Table 5). Results of correlation analysis between callosal atrophy and MRI lesion load showed an association between the total lesion index and all measurements of callosal areas. More interestingly, regional analysis of MRI lesions demonstrated a preferential relationship between lesion indexes for the anterior, middle, and posterior regions of callosal and subcallosal areas and atrophy of the anterior, middle, and posterior callosal subregions (Table 6).

### Table 3. Comparison of Midsagittal Corpus Callosum Area in Patients With Multiple Sclerosis (MS) and Controls at Baseline and Year 5

<table>
<thead>
<tr>
<th>Callosal Areas</th>
<th>Controls (n = 53)</th>
<th>Patients With MS (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline†</td>
<td>Year 5‡</td>
</tr>
<tr>
<td>Total area</td>
<td>796.10 (110.18)</td>
<td>642.67 (116.3)</td>
</tr>
<tr>
<td>A1</td>
<td>97.13 (18.16)</td>
<td>83.86 (17.88)</td>
</tr>
<tr>
<td>A2</td>
<td>84.48 (14.66)</td>
<td>71.86 (16.29)</td>
</tr>
<tr>
<td>A3</td>
<td>225.76 (43.6)</td>
<td>171.74 (33.87)</td>
</tr>
<tr>
<td>P1</td>
<td>88.19 (19.12)</td>
<td>67.43 (17.9)</td>
</tr>
<tr>
<td>P2</td>
<td>85.25 (19.53)</td>
<td>72.78 (16.41)</td>
</tr>
<tr>
<td>P3</td>
<td>225.76 (43.6)</td>
<td>169.28 (32.2)</td>
</tr>
</tbody>
</table>

*All values are expressed as means (SDs).† All values are \( P < .001 \) by t test for comparison of patients with MS and controls at baseline.‡ All values are \( P < .001 \) by t test for comparison of patients with MS between baseline and year 5.

### Table 4. Correlation Between Functional Performances and Callosal Areas at Baseline and Year 5

<table>
<thead>
<tr>
<th>Callosal Areas</th>
<th>Dichotic Listening Test</th>
<th>Sensory Transfer Test</th>
<th>Motor Transfer Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Year 5</td>
<td>Baseline</td>
</tr>
<tr>
<td>Total area</td>
<td>0.001 (−0.50)</td>
<td>0.01 (−0.42)</td>
<td>0.001 (−0.50)</td>
</tr>
<tr>
<td>A1</td>
<td>0.02 (−0.38)</td>
<td>0.01 (−0.40)</td>
<td>0.001 (−0.52)</td>
</tr>
<tr>
<td>A2</td>
<td>0.03 (−0.36)</td>
<td>0.02 (−0.38)</td>
<td>0.001 (−0.52)</td>
</tr>
<tr>
<td>A3</td>
<td>0.01 (−0.41)</td>
<td>0.03 (−0.36)</td>
<td>0.001 (−0.52)</td>
</tr>
<tr>
<td>P1</td>
<td>0.03 (−0.36)</td>
<td>0.02 (−0.38)</td>
<td>0.001 (−0.52)</td>
</tr>
<tr>
<td>P2</td>
<td>0.001 (−0.52)</td>
<td>0.001 (−0.05)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*All values are expressed as correlations (Spearman rank correlation coefficients). NS indicates not statistically significant.

### Table 5. Correlation Between Functional Performances and Magnetic Resonance Imaging (MRI) Lesions at Baseline and Year 5

<table>
<thead>
<tr>
<th>MRI Lesions</th>
<th>Total Index</th>
<th>Anterior Index</th>
<th>Middle Index</th>
<th>Posterior Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Test</td>
<td>Baseline</td>
<td>Year 5</td>
<td>Baseline</td>
<td>Year 5</td>
</tr>
<tr>
<td>Dichotic listening</td>
<td>0.001 (0.52)</td>
<td>0.001 (0.52)</td>
<td>0.01 (0.39)</td>
<td>0.01 (0.41)</td>
</tr>
<tr>
<td>Sensory transfer</td>
<td>0.001 (0.53)</td>
<td>0.001 (0.52)</td>
<td>0.01 (0.40)</td>
<td>0.02 (0.37)</td>
</tr>
<tr>
<td>Motor transfer</td>
<td>0.001 (0.52)</td>
<td>0.001 (0.40)</td>
<td>0.001 (0.51)</td>
<td>0.001 (0.50)</td>
</tr>
</tbody>
</table>

*All values are expressed as correlations (Spearman rank correlation coefficients). NS indicates not statistically significant.

### Correlations Between Functional, MRI, and Clinical Measures

There were no significant correlations between baseline CC measures and FT and age \( (P = .09) \) or prestudy relapse rate \( (P = .12) \). However, baseline EDSS scores were correlated with baseline total callosal atrophy \( (P < .04) \), FT impairment \( (P < .01) \), and extent of T2 lesions \( (P = .02) \) (Table 7).

### FOLLOW-UP ANALYSIS

At year 5, the RR course of MS persisted in 23 patients with MS (80%) and no difference was found between baseline and year 5 for annual relapse rate. Patients who had relapses were treated with corticosteroids. Seven patients were on a secondary progressive course of the disease at year 5, but none of them was being treated with
immunosuppressive drugs or serial infusions of corticosteroids during the study.

**CC Atrophy and FT Impairment Progression in Patients With MS**

A significant progression of CC atrophy and FT impairment was noted between baseline and follow-up evaluation (Table 2 and Table 3). During the 5-year study, patients with MS had a significant increase of CC atrophy for each measure explored (P < .01 for total area, P < .02 for anterior subregions, and P < .01 for posterior subregions) and they presented a significant progression of impairment on the dichotic listening task (P = .005), sensory transfer test (P = .003), and motor transfer task (P = .01).

**Correlations Between Clinical, MRI, and Neuropsychological Measures**

No significant correlations were found between baseline CC and FT and age (P = .09) or prestudy relapse rate (P = .12). Because of the semiquantitative method used to assess T2 MRI lesions, it was impossible to compare change in T2 white matter extent between baseline and year 5. Global ANOVA performed at follow-up showed a persistent significant interaction between performance on dichotic listening and sensory tasks and EDSS score (F = 3.82, P < .01), but no significant interaction was found for motor transfer task (F = 1.28, P = .12). A significant interaction was also found between CC morphology and EDSS scores (F = 4.21, P = .006) and between T2 MRI lesion grading and EDSS score (F = 4.02, P = .002). Multiple regression analysis showed no relationship between CC or FT and 5-year relapse rate or the number of corticosteroid courses used during the study. A significant relationship persisted at year 5 between CC atrophy and FT impairment except for the same subregions than baseline results (splenium for sensory and motor transfer tests and midanterior subregion for dichotic listening test) (Table 4). These results confirmed that CC atrophy and FT impairment follow a progressive and parallel evolution during the course of the disease. Correlation studies showed that the extent of T2 MRI abnormalities continued to be associated with FT impairment (Table 5) and to a lesser degree with CC atrophy (Table 6). Moreover, the extent of MRI lesions at year 5 was correlated with the final EDSS score and a significant correlation persisted between CC atrophy and FT impairment and EDSS level evaluated at year 5 (Table 7). Finally, progression of disability evaluated with EDSS was significantly related with progression of CC atrophy and FT impairment and with T2 lesion load.

**Table 6. Correlation Between Callosal Areas and Magnetic Resonance Imaging (MRI) Lesions at Baseline and Year 5**

<table>
<thead>
<tr>
<th>Callosal Areas</th>
<th>MRI Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Index</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Total area</td>
<td>0.001 (−0.52)</td>
</tr>
<tr>
<td>A1</td>
<td>0.01 (−0.40)</td>
</tr>
<tr>
<td>A2</td>
<td>0.01 (−0.41)</td>
</tr>
<tr>
<td>A3</td>
<td>0.001 (−0.51)</td>
</tr>
<tr>
<td>P1</td>
<td>0.01 (−0.41)</td>
</tr>
<tr>
<td>P2</td>
<td>0.01 (−0.40)</td>
</tr>
<tr>
<td>P3</td>
<td>0.001 (−0.51)</td>
</tr>
</tbody>
</table>

* All values are expressed as correlations (Spearman rank correlation coefficients). NS indicates not statistically significant.

**Table 7. Correlation Between Callosal Areas, Functional Performances, Magnetic Resonance Imaging Lesions, and Expanded Disability Status Scale (EDSS) Score at Baseline and Year 5**

<table>
<thead>
<tr>
<th>Variable</th>
<th>EDSS Score at Baseline</th>
<th>EDSS Score at Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callosal area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total area</td>
<td>0.001 (−0.47)</td>
<td>0.002 (−0.44)</td>
</tr>
<tr>
<td>A1</td>
<td>0.01 (−0.37)</td>
<td>0.03 (−0.32)</td>
</tr>
<tr>
<td>A2</td>
<td>0.04 (−0.30)</td>
<td>0.03 (−0.31)</td>
</tr>
<tr>
<td>A3</td>
<td>0.01 (−0.38)</td>
<td>0.003 (−0.43)</td>
</tr>
<tr>
<td>P1</td>
<td>0.03 (−0.33)</td>
<td>0.04 (−0.31)</td>
</tr>
<tr>
<td>P2</td>
<td>0.04 (−0.31)</td>
<td>0.03 (−0.32)</td>
</tr>
<tr>
<td>P3</td>
<td>0.01 (−0.36)</td>
<td>0.02 (−0.44)</td>
</tr>
<tr>
<td>Functional performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotic listening test</td>
<td>0.001 (0.48)</td>
<td>0.001 (0.47)</td>
</tr>
<tr>
<td>Sensory transfer test</td>
<td>0.001 (0.43)</td>
<td>0.002 (0.45)</td>
</tr>
<tr>
<td>Motor transfer test</td>
<td>0.01 (0.38)</td>
<td>0.01 (0.38)</td>
</tr>
<tr>
<td>Total index of lesions</td>
<td>0.02 (0.37)</td>
<td>0.01 (0.38)</td>
</tr>
</tbody>
</table>

* All values are expressed as correlations (Spearman rank correlation coefficients).
tients with MS. The fact that CC atrophy could be de-
ating lesions of callosal and pericallosal regions induce
MRI lesions and support the hypothesis that demyelin-
rophy of CC and FT impairment are both related to T2
axonal loss and wallerian degeneration.15

The relationship between callosal atrophy and de-
gree of white matter lesions evaluated by MRI is un-
clear. Some previous studies have reported a strong
significant interaction of T2 lesions with CC atrophy16,22
with others finding only a weak relationship.37,21 These
conflicting results could be explained by the heteroge-
nity of methods used to assess demyelinating lesions by
MRI. Simon et al11 showed recently that the degree of CC
atrophy was related to T2 lesion MRI volume as well as
to third and lateral ventricle atrophy. On the contrary,
they found no effect of gadolinium-enhancing lesions on
callosal atrophy while the number of enhancing lesions
at baseline was predictive of progression of third ven-
tricle atrophy. In the light of this latter result, it is sur-
prising to consider that the presence of enhancing les-
sions reflected inflammatory activity at the early stage of
the RR MS but did not influence the degree of callosal
atrophy. In contrast, T2 abnormalities that character-
ized probably more chronic demyelinating lesions with
axonal loss were closely related to the degree of CC at-
rophy. Accordingly, our results clearly showed that at-
rophy of CC and FT impairment are both related to T2
MRI lesions and support the hypothesis that demyelin-
ating lesions of callosal and pericallosal regions induce
CC atrophy and interhemispheric involvement in pa-
tients with MS. The fact that CC atrophy could be de-
tected at early stage of MS and in patients without MRI
lesion could argue that CC atrophy represents an early
marker of atrophy in MS.23 However, further studies of
patients with MS seen at an early stage of MS with nor-
mal white matter appearance on standard MRI are needed
to prove that involvement of CC could be related with
early myelin and/or axonal loss. In this way, future stud-
ies using proton magnetic resonance spectroscopy and
new techniques such as magnetization transfer MRI in
patients with MS who have normal white matter appear-
ance and are seen with isolated syndromes suggestive of
MS could document this hypothesis.3,4,8

The relationship between atrophy measures and dis-
ability in MS has been evaluated in other studies, show-
ing a significant link between cerebellar dysfunction and
cerebellar atrophy,9 and between EDSS score and spinal
cord atrophy.9,32 Consistent with a recent report by
Simon et al11 of a significant link between CC, third and
lateral ventricle atrophy, and EDSS score, we found a sig-
nificant relationship between CC measures and EDSS score
at baseline. In the same way, the degree of FT impair-
ment for all modalities explored were correlated with the
EDSS score. This significant interaction between clinical,
functional, and morphological measures and their rela-
tion with T2 MRI lesions suggests that a destructive patho-
logic process is already present at the early stage of RR MS.

Longitudinal studies of brain atrophy in MS are rare.3,11,33 Results of our longitudinal evaluation showed
that CC atrophy and FT impairment observed at base-
line increased significantly at year 5 in the MS group. At
follow-up, a significant interaction also persisted be-
tween functional scores on interhemispheric transfer and
CC measures, and T2 lesion load was significantly re-
lated with degree of FT impairment and CC atrophy.
Moreover and as already noted at baseline, the level of
disability was linked to FT impairment and CC atrophy
at year 5. Because of the small number of patients in-
cluded in this study, it was impossible to compare FT and
CC means in MS subgroups with high and low levels of
clinical disease activity. The lack of interaction between
callosal involvement and other clinical measures such as
relapse rate, confirm the poor value of these clinical vari-
ables as prognostic markers in patients with RR MS.11,13,33
Moreover, because of the absence of relationship be-
tween treatment of relapses and CC atrophy or FT im-
pairment, corticosteroids do not seem to be a contribut-
ing factor to callosal involvement. Finally, our results
indicate that the major factor influencing CC atrophy and
FT impairment either at baseline or at follow-up was T2
lesion load.

To further investigate the predictive value of callo-
sal involvement in MS, another possibly fruitful avenue
would be to explore the relationship between CC atro-
phy or FT impairment and neuropsychological dysfunc-
tions. Although clinically apparent callosal disconnec-
tion has been rarely reported,34 some prior studies
demonstrated that global cognitive dysfunction, as well
as intellectual and memory disturbances were associ-
ated with a significant increase of ventricular width.35,37
More recently, focal atrophy of the anterior part of the
CC has been related to verbal fluency impairment.19,21 In
particular, according to evidence showing that CC may
play a key role in between-hemisphere facilitation that
maintains bilateral cerebral arousal,26 future studies should
focus on the relationship between attentional dysfunc-
tion, which is frequently reported in patients with MS,30,40
and CC atrophy and MR abnormalities41 to determine the
natural history of callosal involvement in MS. Finally, the
present results provide strong arguments for using ana-
tomical and functional callosal measurements as key
indexes for future evaluations of treatments susceptible
of exerting a preventive effect on the natural history of
MS.42-45

Accepted for publication October 2, 2000.
This investigation was supported in part by grants from
ARSEP (Association pour la Recherche sur la Scle´rose en
Plaques), and PHRC1994-CA3844-UF-1628, from the

Corresponding author: J. Pelletier, MD, PhD, Depart-
ment of Neurology. CHU Timone, F-13385 Marseilles 5,
France (e-mail: jpe pelletier@ap-hm.fr).

(Reprinted) Arch Neurol/Vol 58, Jan 2001 www.archneurol.com
REFERENCES


