Quality of Life and Its Relationship to Brain Lesions and Atrophy on Magnetic Resonance Images in 60 Patients With Multiple Sclerosis

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**Context:** Disease-modifying multiple sclerosis (MS) therapeutic trials continue to rely on physical disability as the main clinical outcome measure, while the impact of treatment on quality of life (QOL) is poorly understood. Weak correlations exist between physical disability and the disease burden as shown using conventional brain magnetic resonance imaging (MRI), indicating poor sensitivities of these measures alone in defining the clinical course of MS.

**Objectives:** To investigate the impact of MS on QOL; to determine whether impaired QOL in patients with MS was related to any regional brain abnormalities assessed using conventional MRI sequences; and to determine if the severity of MS as assessed by the Expanded Disability Status Scale (EDSS) and clinical course was associated with worsening QOL.

**Design, Setting, and Patients:** Prospective, cross-sectional study of 60 consecutive patients with MS treated in a community-based, university-affiliated MS clinic.

**Main Outcome Measures:** Assessments of QOL using the Multiple Sclerosis Quality of Life–54 Instrument were correlated with the scores of the EDSS, clinical course, and findings on brain MRI.

**Results:** Quality of life was significantly impaired in patients with MS and was worse in patients with secondary-progressive MS compared with those with relapsing-remitting MS. Brain MRI lesions and atrophy were associated with impaired QOL with respect to sexual dysfunction, overall mental health, and limitations due to physical and emotional dysfunction. Correlations between MRI results and QOL assessments were much stronger for hypointense lesions and atrophy on T1-weighted images than for hyperintense lesions on T2-weighted images and were insignificant for lesions on contrast-enhanced images. Higher EDSS scores were associated with impairments in most physical and mental health QOL scales but were weakly correlated with cognitive and sexual dysfunction.

**Conclusions:** In patients with MS, QOL is impaired and is associated with increasing neurologic disability. Quality of life assessments are related in part to brain lesions and atrophy shown on MRI. Assessments of QOL provide unique information not readily evaluated by EDSS and may be useful as secondary clinical outcome measures.

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**PHYSICAL DISABILITY assessment using the Expanded Disability Status Scale (EDSS) is currently considered to be the most useful clinical measure of multiple sclerosis (MS) disease activity and is the primary clinical outcome measure in most MS clinical trials.** However, EDSS is heavily influenced by limb and gait dysfunction and may have low sensitivity in detecting other important clinical deficits caused by MS of the brain, such as fatigue, depression, and sexual and cognitive dysfunction. This low sensitivity may partly explain the poor relationship between the assessment of the clinical status of patients using EDSS and the disease burden using conventional brain magnetic resonance imaging (MRI). Hence, there is a need for more sensitive clinical outcome measures that assess the clinical consequences of brain lesions caused by MS. Quality of life (QOL) scales are comprehensive clinical measures that assess several important domains of health from a patient’s perspective and have the potential for being useful clinical outcome measures in the short-term evaluation of disease-modifying drug therapies. However, the effect of MS on various aspects of QOL and the relationship between increasing neurologic disability and pathologic brain alterations and impaired QOL are still not clearly understood.

The purposes of this study were to investigate the impact of MS on QOL and to

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PATIENTS AND METHODS

PATIENT SELECTION AND CLINICAL ASSESSMENT

During a 2-year period, we prospectively interviewed and obtained MRI scans in consecutive patients with clinically definite MS who were referred from the Buffalo, NY, metropolitan area to our community-based clinic. Of 106 patients ages 18 to 60 years, we excluded patients with any of the following: (1) primary-progressive MS (n=3); (2) poor-quality MRI scans (n=5); (3) unwillingness to participate (n=4); (4) other major neurologic and/or systemic diseases (n=10); (5) exacerbations in the previous 4 weeks (n=5); or (6) active substance abuse (n=5).

Fatigue and depression are common in patients with MS. Fifty-eight patients in this study were also included in other recently reported studies on the correlation between fatigue and MRI results and between fatigue and depression. To study as directly as possible the relationship between QOL and the disease process of MS, we excluded patients taking medications in the past 2 months that might affect fatigue, mood, or cognition and thereby alter QOL.14-16 Many of the patients included in this study had fatigue or depression but were not taking any psychoactive medications since most of them had been recently diagnosed as having MS. These patients subsequently began taking appropriate medications after data collection. Further study of interrelationships between fatigue, depression, and QOL in these patients is ongoing at our center.

Interferon beta has been implicated as a cause of depression in patients with MS. As most of the subjects included in this study were patients with newly diagnosed or previously untreated relapsing-remitting MS (RRMS) or with secondary-progressive MS, there were only 4 patients with RRMS who were taking interferon beta-1a (n=2) or interferon beta-1b (n=2) at the time of data collection. Neuropsychologic interviews using the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition revealed that none of the patients taking interferon beta included in the present study had depression.

RESULTS

CLINICAL ASPECTS

Assessments of QOL were associated with the severity of neurologic disease from several perspectives. First, patients with secondary-progressive MS had significantly lower QOL scores than those with RRMS. This difference was seen across a variety of QOL scales and was most robust for physical function (Table 1). Second, increased neurologic disability measured by EDSS significantly correlated with decreased QOL across a variety of QOL scales (Table 2 and Figure 2). However, the correlations between EDSS scores and cognitive and sexual dysfunction were not robust (Table 2). The MSQOL-54 scores also did not show any significant relationship with age, sex, or disease duration (data not shown).

We compared the MSQOL-54 profiles in our study group with the Los Angeles, Calif, study group as the populations were similar in age and sex. We also compared the mean generic QOL scores of both the study groups with the Short Form 36-Item Health Survey QOL scores of a sample US population with similar age and sex (the general population data are those of 2474 respondents to the 1990 National Survey of Functional Health Status). There were no significant variations in MSQOL-54 scores between the 2 populations with MS. However, there was a marked decrease in QOL of pa-

There were 60 patients, with a mean age of 42 years (range, 27-60 years), included in the study. Forty-two patients were women. The mean duration of MS was 10.2 years (range, 6 months to 43 years). The clinical subtype was categorized as RRMS (n=42) or secondary-progressive MS (n=18). Neurologic disability was assessed by a single experienced neurologist (R.B.) using the EDSS.14 We examined 54 patients (90%) using the EDSS, clinical interviews, the QOL questionnaire, and MRI on the same day. We examined the other 6 patients using the EDSS, clinical interviews, and the QOL questionnaire within 1 month of the MRI examination, and these patients were interviewed to ensure clinical stability between MRI and QOL assessments.

QOL ASSESSMENT

We chose the Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument, developed by Vickrey et al as the quantitative measure of QOL in our study. This QOL questionnaire has the advantage of both generic as well as MS-specific QOL assessments. It has been shown to have high test-retest reliability (intraclass correlation coefficients, 0.66-0.96) and high internal consistency (0.75-0.96), with evidence supporting its content and construct validity. An Italian version of the MSQOL-54 Instrument has also been recently validated. The MSQOL-54 Instrument comprises questions from the Short Form 36-Item Health Survey as a generic core measure, which enables comparisons of the QOL of patients with MS with existing QOL data for the general population (Figure 1, top). To enhance comparisons within groups of patients with MS, the MSQOL-54 Instrument has 18 additional items that are specific to MS (Figure 1, bottom). In total, the 54 items in the questionnaire are distributed into 12 multi-item scales and 2 single-item scales. Scale scores were created by averaging the items within scales and transforming the mean scores linearly to 0 to 100 possible scores, with higher scores indicating a better QOL. Physical and mental health composite scores were also calculated as a weighted sum of selected scales to generate a simplified 2-factor solution to the MSQOL-54 Instrument. (QOL scales used to calculate each of these composite scores are shown in Table 1.) However, since individual QOL scales have also been shown to have valid psychometric properties and provide useful information...
not readily captured by the generalized composite scores,16,17 we used individual QOL scales in addition to the composite scores in this study.

NEUROIMAGING

Axial fast spin-echo 1.5-T MRI was performed using 5-mm interleaved T1-weighted images, T2-weighted images, proton-density-weighted images, and fluid-attenuated inversion recovery sequences. Thirty-seven patients were studied using contrast-enhanced T1-weighted images. Two observers (V.J. and R.B.) masked to clinical details visually rated the MRI scans by consensus, based on a previously detailed method.10 All axial slices were analyzed for lesions and atrophy in the following regions: superior and inferior frontal lobes, superior and inferior parietal lobes, occipital and temporal lobes, cerebellum, midbrain, and pons. Standard sulci and fissures were used to separate the lobes, including the central sulcus, lateral fissure, and parieto-occipital sulcus. The third ventricle demarcated superior vs inferior frontal or parietal lobes. The severity of hypointense lesions on T1-weighted images and hypointense lesions on non–contrast-enhanced T1-weighted images was assessed. We used an ordinal rating system that assessed the severity of lesions in each region based on the percentage of involvement (total lesion volume proportional to entire size of that region). The hypointense lesions on T2-weighted images were ordinarily rated by severity according to percentage of involvement of the entire region as mild (<25%), moderate (25%-50%), or severe (>50%). As hypointense lesions on T1-weighted images are markers of more severe demyelination and axonal loss,19 they were ordinarily rated as mild (<10%), moderate (10%-25%), or severe (>25%). To increase confidence in lesion detection, lesion brightness compared with gray matter on T2-weighted images was confirmed by proton-density-weighted images and fluid-attenuated inversion recovery sequences. Contrast enhancement was assessed by counting the number of lesions. Evidence of atrophy was assessed by ordinarily rating the enlargement of subarachnoid spaces in the above-mentioned regions as well as rating the enlargement of the ventricular cavities (lateral ventricles: body, frontal, temporal and occipital horns, and third and fourth ventricles) on non–contrast-enhanced T1-weighted images. Atrophy was rated and compared with age- and sex-matched controls obtained from a pool of 100 consecutive normal scans of patients in whom MS was excluded clinically. We have previously detailed our method of obtaining this normative MRI database.19 Each patient’s scan was rated against a control’s scan for atrophy. The degree of atrophy was ordinarily rated as normal (0%), mild (<10%), moderate (10%-25%), or severe (>25%), according to the percentage of volume loss of parenchyma or percentage of ventricular size increase. In a randomly chosen subset of 27 patients in this study who were rated 1 month later without knowledge of previous ratings, intraobserver agreement of this MRI analysis technique was generally very good (mean κ = 0.9 [range, 0.8-1.0]); interobserver agreement was generally moderate to very good (mean κ = 0.8 [range, 0.6-1.0]).

STATISTICAL ANALYSIS

Correlation of MSQOL-54 scores with age, disease duration, and EDSS was assessed for all 60 patients, using the Spearman rank correlation test. Differences in MSQOL-54 scores between groups (sex and MS clinical course) were assessed by the Mann-Whitney U test. P < .01 was considered significant (2-tailed), and P < .05 was considered a significant trend. Variable selection techniques were used to select MRI findings that were predictive of each individual QOL measure. Because of the large number of variables tested, P < .05 in the result of Spearman rank correlation test was used as a screening criterion. Regression model building was performed using stepwise forward regression, adjusted r², and Mallows Cp criteria. Values of Akaike Information Criteria and Schwartz-Bayesian Information Criteria were compared for plausible statistical models. Models with significant negative regression coefficients, with acceptable Akaike Information Criteria and Schwartz-Bayesian Information Criteria, were considered as final regression models. Standard diagnostic plots were used to check the validity of the models. Reported P values for regression coefficients in the final models were not adjusted for the number of models considered because of the exploratory nature of the analysis. We used SAS (SAS Institute Inc, Cary, NC) and S-PLUS 2000 (SCIA Group, Herk-de-Stad, Belgium) statistical software for the analysis.

T1-weighted images. Atrophy was rated and compared with age- and sex-matched controls obtained from a pool of 100 consecutive normal scans of patients in whom MS was excluded clinically. We have previously detailed our method of obtaining this normative MRI database.19 Each patient’s scan was rated against a control’s scan for atrophy. The degree of atrophy was ordinarily rated as normal (0%), mild (<10%), moderate (10%-25%), or severe (>25%), according to the percentage of volume loss of parenchyma or percentage of ventricular size increase. In a randomly chosen subset of 27 patients in this study who were rated 1 month later without knowledge of previous ratings, intraobserver agreement of this MRI analysis technique was generally very good (mean κ = 0.9 [range, 0.8-1.0]); interobserver agreement was generally moderate to very good (mean κ = 0.8 [range, 0.6-1.0]).

Magnetic resonance imaging is considered a standard method for diagnosing MS of the brain23 and spine,24 and its high sensitivity to MS disease activity has also led to its use as a surrogate marker of treatment effect in clinical trials.25,26 However, weak correlations exist between disease burden shown on conventional brain MRIs and clinical disease severity assessed by EDSS.9 One pos-
sible explanation for this paradox lies in the low sensitivity of EDSS in assessing the heterogeneous clinical manifestations of MS of the brain. Since EDSS scores are heavily influenced by limb and gait dysfunction, a need for multidimensional clinical outcome measures, such as QOL scales that assess other important aspects of MS of the brain, such as fatigue, depression, and sexual and cognitive dysfunction, has been recognized. The EDSS is also a composite scale comprising 8 functional systems with individual grades that assess various aspects of neurologic impairment. Since most MS clinical trials continue to use the EDSS score as the primary outcome measure compared with the individual functional systems grades, we decided to compare EDSS scores with QOL measures. However, future studies should assess whether individual functional systems grades show stronger correlations with QOL and MRI assessments of disease burden. The results of this study indicate that QOL

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Figure 1. Top, A comparison of the mean scores of the Short Form 36-Item Health Survey (generic scales) of patients with multiple sclerosis (MS) from 2 different groups in the United States—Buffalo, NY (present study), and Los Angeles, Calif (previous study)—with data from the general US population. Bottom, A comparison of the mean quality of life scores (MS-specific scales and physical and mental health composite scores) of patients with MS from the present study and a previous study.

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is severely impaired in patients with MS compared with the general population, and this finding may be related in part to brain MRI assessments of disease burden.

Regional white matter lesions and atrophy shown on MRIs were significantly associated with worsening QOL in patients with MS in our study with respect to sexual dysfunction, role limitations due to physical and/or emotional dysfunction, and impaired overall mental health. White matter lesions in the inferior parietal lobe, pontine atrophy, and enlargement of the lateral ventricles were significantly associated with sexual dysfunction in patients with MS. An animal study27 showed that sexual behavior is severely impaired in patients with MS compared with the general population, and this finding may be related in part to brain MRI assessments of disease burden.

Patients with MS commonly had difficulty with regular daily activities and had problems at work as a direct consequence of physical and emotional dysfunction. Hypointense lesions on T1-weighted images in the superior parietal lobe were significantly associated with role limitations due to physical and/or emotional dysfunction and impaired overall mental health. Atrophy of the temporal lobe was also associated with role limitations due to physical dysfunction. These results suggest that impaired mental health, emotional dysfunction, and a patient’s perception of physical disability may all be related in part to dysfunction of serotonergic “emotional” pathways in cortical, thalamic, and limbic circuits.29 A recent functional MRI study30 on emotional arousal indicated that processing emotions requires the activation of the inferior and superior parietal lobules, the right fusiform gyrus, and the bilateral occipital gyri. This finding may explain why atrophy of the occipital lobe was associated with role limitations due to emotional dysfunction in patients in the present study. Our study has also shown that increasing neurologic disability is significantly related to worsening overall physical and men-
nal health of patients with MS. In addition, QOL assessments were significantly lower in patients with secondary-progressive MS compared with patients with RRMS, suggesting that QOL significantly declines with disease progression.

Although lower QOL assessments are associated with increasing neurologic disability and regional lesions and atrophy on conventional brain MRIs, the correlations between brain MRI disease burden and QOL assessments still remain weak. The weakest association between MRI abnormalities and QOL was for T2 hyperintense lesions and contrast-enhanced lesions. Hyperintense lesions on T2-weighted images are nonspecific for the extent of tissue injury in MS plaques, precluding the differentiation between potentially mild or reversible changes and those causing more severe tissue injury or fixed dysfunction (axonal loss or degeneration).11 Contrast-enhancing MRI lesions represent transient blood-brain barrier dysfunction and do not necessarily predict the development of persistent deficits.12 These findings may explain the weak correlations of lesions shown on T2 hyperintense and contrast-enhanced lesions with clinical disability in previous studies4,31,32 and the similar weak correlation with QOL in the present study. However, marked hypointense lesions ("black holes") on T1-weighted images represent more specific long-term irreversible tissue changes, such as hypocellularity, severe demyelination, and axonal loss.13 Axonal transection occurs commonly in brains of patients with MS, and this axonal damage may be the pathologic correlate of irreversible neurologic impairment.33 Progressive axonal damage may contribute to the macroscopic brain atrophy shown on MRI.34 This atrophy correlates well with neurologic disability,35 depression,36 clinical deterioration,37 and brain hypometabolism shown by positron-emission tomography.38 Therefore, the much stronger association between hypointense lesions and atrophy on T1-weighted images and QOL assessments compared with lesions shown on T2-weighted or contrast-enhanced images may relate to the higher specificity of these techniques for showing neuropathologic damage and subsequent brain dysfunction in MS.19,39 Consistent with this hypothesis, hypointense lesions and atrophy in the brain on T1-weighted images are more closely related to depression in patients with MS than hyperintense lesions on T2-weighted images.35

The major strengths of our study are the following: we administered the MRI and QOL assessments on the same day or within a month; a single observer assessed the EDSS; we used careful selection criteria to ensure that alterations in QOL were due to MS; and we obtained a comprehensive assessment of QOL using a validated scale. Data showing validity of this MRI rating method for measuring atrophy and lesions in patients with MS are being prepared for separate publications. Intraobserver reliability of this MRI method in the patients in the present study was generally very good; interobserver reliability was generally moderate to very good. Other clinically relevant neuroimaging measures of tissue injury in MS are emerging, such as magnetization-transfer measurement,38 magnetic resonance spectroscopy,39 diffusion tensor imaging,40 positron emission tomographic functional imaging,41 and assessment of spinal lesions22,42 and spinal atrophy.43 Another aspect of the MS process not assessed by the present study is the T2 shortening that has been described in cortical and subcortical gray matter on T2-weighted MRI scans ("black T2" lesions) that correlates with physical disability in patients with MS.44 These hypointense lesions on T2-weighted images may indicate pathologic iron deposition due to neuronal degeneration and may have clinical significance.44 Finally, computer-assisted measures of lesion load45 and atrophy37,46

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<th>Table 3. Regional Abnormalities on Magnetic Resonance Images (MRIs) Predictive of Impaired Quality of Life in 60 Patients With Multiple Sclerosis*</th>
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<td><strong>MSQOL-54 Scales</strong></td>
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*P values indicate the significance of the t statistic in a linear regression model predicting the score on the Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument.44 T1 hypointense lesions in the superior parietal lobe (SPL) and atrophy in the occipital lobe (OL) were independently predictive of role limitations due to emotional dysfunction. TL indicates temporal lobe; IPL, inferior parietal lobe; and LVB, lateral ventricular bodies.
are being used to quantitate MRI abnormalities in patients with MS. These techniques will likely improve the understanding of how the MS disease process in the central nervous system affects QOL.

In conclusion, the assessments of QOL in patients with MS are markedly lower in comparison to the general population, are related to increased clinical disease severity, and are partly related to lesions and atrophy shown on brain MRI scans. Patient-assessed QOL scales provide unique information not readily assessed by physician-derived disability scales and could serve as useful secondary clinical outcome measures in phase 3 MS clinical trials. Further study is necessary to better understand how the MS disease process affects QOL.

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