

Comparison of Quality of Life in Clinically Isolated Syndrome Patients Who Convert and Do Not Convert to Clinically Definite Multiple Sclerosis

Deborah M. Miller, PhD; Craig Kollman, PhD; Andrea Kalajian, MS;
Paul W. O'Connor, MD; R. Philip Kinkel, MD

*A secondary analysis was undertaken to compare patient-reported outcomes (PROs) of individuals who did and did not convert to clinically definite multiple sclerosis (CDMS) approximately 5 years after their first clinically isolated syndrome (CIS). Patients included in the analysis were participating in a long-term extension (called CHAMPIONS) of the Controlled High-Risk Avonex® Multiple Sclerosis Prevention Study (CHAMPS). The Multiple Sclerosis Quality of Life Inventory (MSQLI), a battery including the Short Form Health Status Survey (SF-36) and nine disease-specific scales, was administered to participants 5 years after their initial symptoms suggestive of MS (randomization into the CHAMPS study). Of 203 CHAMPIONS patients, 188 (93%) completed the MSQLI at enrollment into this extension study. Of these, 79 (42%) converted to CDMS. Statistically significant differences ($P < .001$) between those who did and did not convert to CDMS were found for 4 of the 11 MSQLI scales: the SF-36 Physical Component Summary, the Modified Fatigue Impact Scale, the Pain Effects Scale, and the Bladder Control Scale. Trends not meeting our criteria for statistical significance ($P > .001$ but $< .01$) were observed for the SF-36 Mental Component Summary, the Perceived Deficits Questionnaire, and the Mental Health Inventory. SF-36 scores for patients not converting to CDMS over 5 years were similar to those reported for age-matched normal controls. No other demographic or disease-related factors were associated with these PROs. When stratified by Expanded Disability Status Scale score, patients who converted to CDMS demonstrated statistically significant differences on the same four scales defined above that differentiated those who did and did not convert to CDMS. These data show that individuals who have CDMS but limited disability demonstrate clear evidence of diminished health-related quality of life. *Int J MS Care*. 2009;11:17–24.*

Multiple sclerosis (MS) is a chronic progressive disease of the central nervous system that frequently begins as a clinically isolated demyelinating syndrome (CIS) of the optic nerve, brainstem and cerebellum, or spinal cord. Patients at high risk of developing clinically definite multiple sclerosis (CDMS) are identified after a CIS by the presence of

characteristic white-matter lesions on magnetic resonance imaging (MRI) of the brain and spinal cord. Many patients go for years after the first attack without experiencing another attack sufficient for a diagnosis of CDMS.¹ These patients are referred to as having “possible MS” according to international diagnostic criteria.² Few patients who experience a CIS, regardless of conversion to CDMS status, demonstrate measurable disability within 5 years of that first attack, but many describe persistent or recurrent symptoms related to the initial attack or subsequent attacks.

Evidence exists that recently diagnosed patients with a variety of diseases experience a reduction in well-being,

From the Cleveland Clinic, Cleveland, OH, USA (DMM); Jaeb Center for Health Research, Tampa, FL, USA (CK, AK); St. Michael's Hospital, Toronto, Ontario, Canada (PWO); and Beth Israel Deaconess Medical Center, Boston, MA, USA (RPK). Correspondence: Deborah M. Miller, PhD, Associate Professor of Medicine, Cleveland Clinic, Mellen Center/U-10, 9500 Euclid Ave., Cleveland, OH 44195; e-mail: MILLERD@ccf.org.

including patients with diabetes,³ Graves' disease,⁴ and Parkinson's disease.⁵ Although the negative impact of MS on patient-reported outcomes (PROs) has been well documented in individuals with CDMS living with moderate-to-severe disability,^{6,7} the PRO consequences for individuals who are at risk of developing MS or who recently converted to CDMS have not been described. Patients who have experienced a CIS may live with residual limitations and symptoms from that first neurologic attack. Those who do develop CDMS live with the consequences of that first exacerbation as well as subsequent disease activity. Here we focus on the residual symptoms and impairments experienced by patients with a CIS and CDMS. According to the World Health Organization, although limitations and symptoms may interfere with aspects of patients' reported daily functioning, this does not necessarily imply that these difficulties result in disabilities.⁸

The Controlled High-Risk Avonex[®] Multiple Sclerosis Prevention Study (CHAMPS), a randomized controlled trial, demonstrated that intramuscular interferon β -1a (IM IFN β -1a) significantly slows the rate of development of CDMS over a 2-year period. The Controlled High-Risk Avonex[®] Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance (CHAMPIONS) is an ongoing investigator-initiated open-label study that allows further monitoring of those study participants. Patients were enrolled in CHAMPIONS after completion of CHAMPS and reevaluated 5 years after the onset of their first neurologic symptoms suggestive of MS (ie, when they entered CHAMPS). A major reason for conducting this add-on study was to determine whether immediate initiation of IM IFN β -1a after a CIS is more effective than delayed treatment. Details of CHAMPIONS have been reported elsewhere.⁹

The Multiple Sclerosis Quality of Life Inventory (MSQLI) was administered to subjects at the 5-year evaluation. The MSQLI is a commonly used MS-specific health-related quality of life (HRQL) measure developed under the sponsorship of the National Multiple Sclerosis Society and the Consortium of Multiple Sclerosis Centers. It was developed and validated in a group of 300 patients with MS who spanned the continuum of MS disability.¹⁰ It has undergone additional psychometric assessment in patients with secondary progressive MS,¹¹ elderly people with MS,¹² and people with MS who demonstrated cognitive impairment.¹³ The MSQLI has been used as an outcome measure in trials of IFN β -

1a in secondary progressive MS¹⁴ and in patients with MS who are undergoing rehabilitation after an exacerbation of their disease.¹⁵ It was included in the CHAMPIONS trial to assess the relative consequences of a CIS and CDMS in individuals who are in the very early stages of neurologic dysfunction.

Using the 5-year analyses data from CHAMPIONS and the MSQLI, we evaluated the PRO status of this cohort. We compared individuals who remained classified as CIS with those who converted to CDMS on a number of clinical and demographic variables.

Materials and Methods

Methods

This was a cross-sectional analysis of data obtained from patients at their 5-year evaluation in the CHAMPIONS study (ie, approximately 5 years after their first neurologic symptoms suggestive of MS).

Patients

In all, 203 of the original 383 CHAMPS study patients enrolled in the CHAMPIONS study. The protocol and informed consent forms were approved by the institutional review boards at each study site, and all patients gave written informed consent to participate. All 203 CHAMPIONS participants were eligible for this study.

Clinical Outcome Measures

The primary end point in the CHAMPIONS study was conversion to CDMS as determined by an independent, blinded outcomes committee. This conversion could occur at any time during the 5-year period of the CHAMPS and CHAMPIONS studies. Participants were assessed on a number of variables, described below.

Conversion to CDMS was stratified by the receipt of immediate treatment (the original treatment group in the CHAMPS study) and the receipt of delayed treatment (the original placebo group in the CHAMPS study). In a separate stratification, patients who converted to CDMS were compared with those who did not.

Cranial MRI data of the brain were also collected at entry into the CHAMPIONS study. Evidence of new or enlarging lesions on T2-weighted images is an indicator of MS disease activity. The numbers of new or enlarging T2 lesions at 5 years compared with CHAMPS baseline MRI data were stratified into groups with no lesions, one to four lesions, and five or more lesions.

The Expanded Disability Status Scale (EDSS) is a commonly used MS disability rating scale that is based on standard neurologic examination. It is an ordinal scale measured in half-point increments, with 0 indicating a normal neurologic exam and 10 representing death. In this group of limited-disability individuals, EDSS scores from 0 to 1.5 indicate minimal impairment, scores from 2 to 2.5 indicate mild impairment, and scores of 3 or above indicate mild-to-moderate impairment. The EDSS scores used for these analyses are those from the 5-year evaluation in the CHAMPIONS study. Demographic factors including sex and age are included in the analyses.

PRO Outcome Measure

The MSQLI includes the well-known generic Medical Outcomes Study Short Form Health Status Survey (SF-36) as well as nine disease-specific measures and is reported as 11 scale scores. Details of the MSQLI results are reported in Table 1.

Statistical Analysis

Because of ceiling/floor effects, values for some of the MSQLI scales did not follow a normal distribution. Univariate analyses associating MSQLI scores with disease and demographic factors were therefore performed using rank tests. The Kruskal-Wallis test was used for discrete variables, and the Spearman correlation was used for continuous variables. Associations between EDSS and MSQLI scores were performed separately for patients with and without CDMS by 5 years. Because these analyses were conducted for each of the 11 MSQLI scales (multiple comparisons), *P* values between .01 and .001 were considered suggestive, and only *P* values < .001 were regarded as conclusive.

Differences in MSQLI score stratified by EDSS scores at 5 years in CHAMPIONS were calculated for those patients who had converted to CDMS and those who had not. This analysis was conducted to determine whether differences in EDSS status resulted in comparable impact on MSQLI scores for the CDMS and non-CDMS groups.

Results

Demographics

Of the 203 patients enrolled in CHAMPIONS, 8 patients missed the 5-year visit, 6 patients completed the visit out-of-window (range, 5.6–6.2 years; 3 with and 3 without CDMS), and 1 patient completed the visit but

Table 1. Description of Multiple Sclerosis Quality of Life Inventory

Scale	No. of items	Range of possible scores
SF-36 Physical Component Summary ¹⁶	18	0–100 ^a
SF-36 Mental Component Summary ¹⁶	18	0–100 ^a
MFIS ¹⁷	10	0–84 ^b
PES ¹⁸	6	6–30 ^b
SSS ¹⁹	4	4–24 ^b
BLCS ^c	4	0–22 ^b
BWCS ^c	5	0–26 ^b
IVIS ^c	5	0–15 ^b
PDQ ²⁰	20	0–80 ^b
MSSS ²¹	18	0–100 ^a
MHI ²²	18	0–100 ^a

Abbreviations: BLCS, Bladder Control Scale; BWCS, Bowel Control Scale; IVIS, Impact of Visual Impairment Scale; MFIS, Modified Fatigue Impact Scale; MHI, Mental Health Inventory; MSSS, Modified Social Support Survey; PDQ, Perceived Deficits Questionnaire; PES, Pain Effects Scale; SF-36, Short Form Health Status Survey; SSS, Sexual Satisfaction Scale.

^aHigher score indicates better functioning.

^bLower score indicates better functioning.

^cDeveloped for use in the Multiple Sclerosis Quality of Life Inventory.

was not offered the MSQLI. The MSQLI was administered to the remaining 188 patients (93%). The median age of these 188 patients at CHAMPS randomization was 34 years (range, 20–54 years); 141 (75%) were female; 169 (90%) were white. At the time of the 5-year analysis of CHAMPIONS, 79 (42%) patients had converted to CDMS. For the 79 patients in the CDMS group, the EDSS score was less than or equal to 1 for 24 (30%) patients, between 1.5 and 2.5 for 36 patients (46%), and 3 or above for 19 patients (24%) (Figure 1). Corresponding results for the 109 patients without CDMS were 77 (71%), 27 (25%), and 5 (5%) (Figure 2).

As shown in Table 2, CDMS status was the only statistically significant determinant of differences in MSQLI scores. Patients in the CDMS group had a statistically significant (*P* < .001) decrement compared with patients in the non-CDMS group on 4 of the 11 scales: the SF-36 Physical Component Summary (PCS), the Modified Fatigue Impact Scale, the Pain Effects Scale,

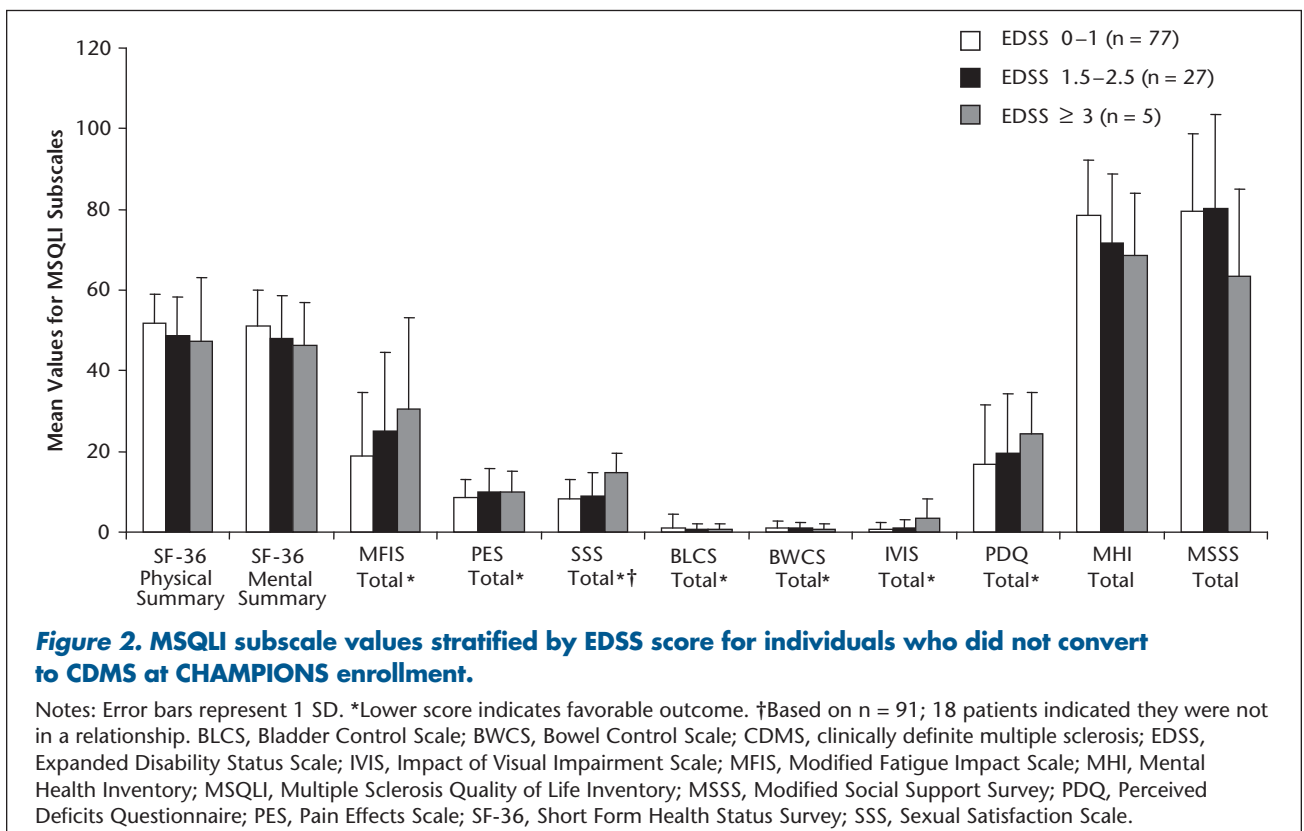
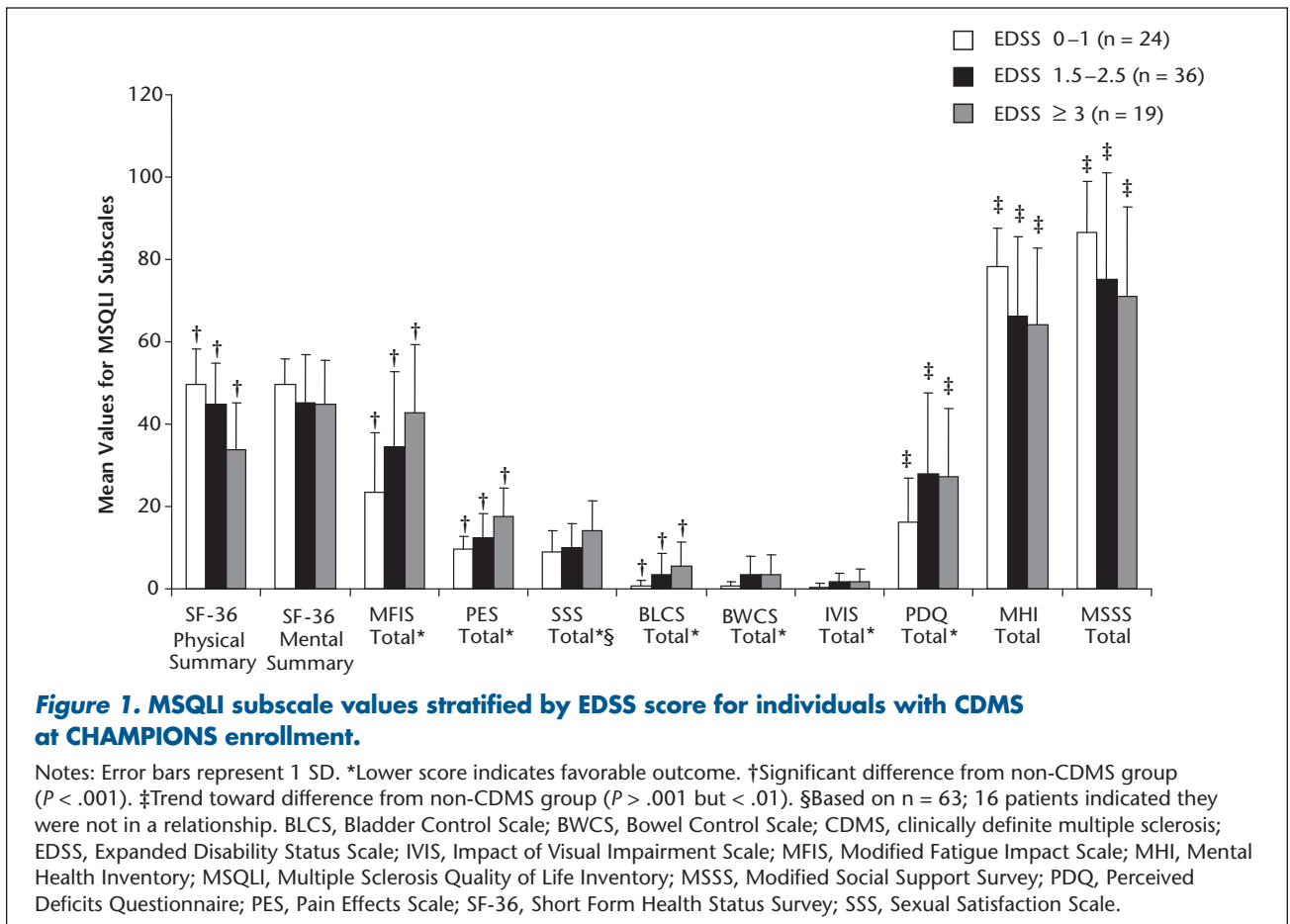


Table 2. Univariate analysis of Multiple Sclerosis Quality of Life Inventory scales with demographic and disease characteristics

Factor	N	SF-36 ^a Physical Summary Score	SF-36 ^a Mental Summary Score	MFIS ^b Total Score	PES ^b Total Score	SSS ^b Total Score	BLCS ^b Total Score	BWCS ^b Total Score	IVIS ^b Total Score	PDQ ^b Total Score	MHI ^a Total Score	MSSS ^a Total Score
Overall	188	47.7 (10.5)	48.6 (9.9)	26.0 (18.5)	10.6 (5.7)	9.4 (5.7)	1.9 (3.9)	1.6 (3.1)	1.2 (2.0)	20.5 (16.0)	73.5 (16.4)	78.5 (21.2)
CDMS by 5-year visit												
No	109	50.8 (8.5) ^c	50.2 (9.4) ^d	20.9 (17.2) ^c	9.1 (4.8) ^c	8.7 (5.2)	0.9 (2.8) ^c	0.9 (1.8)	1.0 (1.9)	17.8 (14.7) ^d	76.5 (14.9) ^d	78.9 (20.6)
Yes	79	43.6 (11.7) ^c	46.5 (10.2) ^d	33.0 (18.1) ^c	12.7 (6.2) ^c	10.4 (6.2)	3.1 (4.9) ^c	2.6 (4.1)	1.4 (2.1)	24.3 (17.1) ^d	69.3 (17.6) ^d	77.8 (22.2)
New/enlarging T2 lesions^e												
None	34	47.0 (10.1)	48.6 (8.1)	25.1 (18.2)	10.9 (5.8)	9.1 (4.5)	1.1 (3.2)	1.5 (2.4)	1.1 (1.9)	21.0 (15.5)	72.9 (16.5)	78.4 (21.3)
1–4	57	48.9 (9.9)	49.7 (10.8)	24.1 (18.4)	9.8 (5.2)	8.9 (6.5)	1.9 (4.2)	1.5 (3.2)	0.9 (1.5)	21.7 (16.1)	74.6 (17.4)	78.7 (23.1)
≥5	87	47.3 (11.1)	47.7 (10.2)	27.4 (19.0)	11.2 (6.1)	9.6 (5.3)	2.2 (4.2)	1.6 (3.2)	1.2 (2.2)	19.6 (16.6)	73.1 (15.8)	78.8 (20.6)
Randomization group												
Immediate-treatment group	96	47.4 (10.8)	48.0 (9.2)	26.3 (19.4)	10.8 (5.8)	9.7 (5.9)	1.4 (3.1)	1.5 (2.3)	1.2 (2.1)	21.1 (16.9)	72.8 (16.7)	76.9 (23.2)
Delayed-treatment group	92	48.1 (10.3)	49.2 (10.6)	25.6 (17.7)	10.5 (5.6)	9.0 (5.5)	2.3 (4.6)	1.7 (3.7)	1.2 (1.9)	19.9 (15.2)	74.1 (16.3)	80.1 (19.0)
Sex												
Female	141	47.4 (10.9)	48.3 (10.0)	26.5 (18.6)	10.8 (5.7)	9.7 (6.0)	2.2 (4.2) ^d	1.8 (3.1)	0.9 (1.7)	21.2 (16.3)	72.9 (16.7)	77.7 (20.8)
Male	47	48.8 (9.2)	49.4 (9.7)	24.3 (18.4)	10.1 (5.7)	8.5 (4.6)	0.9 (2.8) ^d	1.2 (3.0)	1.9 (2.6)	18.5 (15.2)	75.1 (15.7)	80.9 (22.5)
Age, yr^f												
<28	36	49.7 (10.4)	48.3 (11.3)	21.9 (19.4)	10.1 (6.3)	9.5 (5.4)	2.2 (4.7)	2.1 (4.2)	0.8 (2.1)	15.6 (15.0)	74.2 (20.1)	84.0 (17.5)
28 to <33	47	48.7 (10.1)	48.5 (11.1)	25.1 (18.7)	10.0 (5.7)	9.7 (6.5)	1.9 (4.0)	1.9 (3.3)	1.0 (1.9)	19.1 (16.2)	72.6 (18.8)	74.9 (24.7)
33 to <39	51	47.0 (10.9)	48.6 (7.9)	27.2 (17.0)	11.2 (5.4)	8.5 (5.2)	1.6 (4.0)	1.6 (3.0)	1.4 (2.1)	22.7 (15.2)	74.9 (10.9)	83.1 (19.9)
≥39	54	46.3 (10.7)	48.9 (9.8)	28.2 (19.3)	11.0 (5.6)	9.8 (5.8)	1.8 (3.3)	1.1 (1.9)	1.4 (1.8) ^d	23.0 (16.9) ^d	72.4 (16.3)	73.5 (20.2)

Abbreviations: BLCS, Bladder Control Scale; BWCS, Bowel Control Scale; CDMS, clinically definite multiple sclerosis; IVIS, Impact of Visual Impairment Scale; MFIS, Modified Fatigue Impact Scale; MHI, Mental Health Inventory; MSSS, Modified Social Support Survey; PDQ, Perceived Deficits Questionnaire; PES, Pain Effects Scale; SF-36, Short Form Health Status Survey; SSS, Sexual Satisfaction Scale.

Note: Data are presented as mean (SD).

^aHigher score indicates better quality of life.

^bLower score indicates better quality of life.

^c $P < .001$.

^d $P > .001$ but $< .01$.

^eData missing for 10 patients; analyzed as a continuous variable.

^fAnalyzed as a continuous variable.

and the Bladder Control Scale. These patients' functioning on the remaining scales was consistently worse than that in the non-CDMS group, with trends ($P > .001$ but $< .01$) observed for the SF-36 Mental Component Summary (MCS), the Perceived Deficits Questionnaire, and the Mental Health Inventory. In contrast, no differences in MSQLI subscales were identified based on type of CIS at onset (ie, optic neuritis, brainstem and cerebellar syndrome, or spinal cord syndrome; data not shown), time of treatment initiation, sex, age, or number of new or enlarging T2 lesions.

When patients with and without CDMS were stratified by EDSS score, patients with CDMS had statistically significantly worse scores on the SF-36 PCS, the Modified Fatigue Impact Scale, the Pain Effects Scale, and the Bladder Control Scale, with poorer outcomes correlated with increasing EDSS score (Figure 1). Trends toward poorer outcomes with higher EDSS scores were observed for the seven additional components of the MSQLI. Similar trends are apparent among patients without CDMS (Figure 2), but these trends did not reach statistical significance.

Discussion

This secondary analysis was conducted to assess factors associated with PROs 5 years after a CIS in patients who had asymptomatic cranial white-matter lesions and who were considered at high risk of developing CDMS. Our primary finding is that the development of CDMS is associated with diminished HRQL, particularly among patients with mild-to-moderate levels of residual disability as assessed by the EDSS.

Although it is generally understood that MS exacerbations leave residual symptoms and impairments,^{23,24} the data reported here indicate that very early in the disease, individuals with CDMS are affected by common MS symptoms—including reduced general physical functioning, fatigue, pain, and difficulty with bladder control—to a greater extent than individuals who have experienced only a CIS. It is not clear why bowel symptoms and sexual satisfaction, often closely associated with bladder symptoms, were not distinguishable between those who did and did not develop CDMS. As vision impairment is a symptom often associated with a CIS, the lack of between-group differences is not surprising. It is expected that with longer observation, additional statistically significant between-group differences, including in level of social support, will become apparent.

The mean SF-36 PCS and MCS scores for patients who did not convert to CDMS by 5 years were comparable to those of the general US population,²⁵ while PCS scores and, to a lesser extent, MCS scores for patients with CDMS indicated a clinically significant reduction in well-being. These results suggest that the prevention of CDMS, by either active early treatment or natural history, was associated with the preservation of relatively normal HRQL as well as minimal residual disability as measured by the EDSS.

Although few patients developed significant disability in this cohort of those with early MS, the development of even mild-to-moderate impairment as measured by the EDSS at 5 years may not demonstrate the full impact of the symptoms that did develop (ie, SF-36 PCS, Pain Effects Scale, Modified Fatigue Impact Scale, and Bladder Control Scale). These findings further validate the presence of important symptom interference early in the disease. Although a close association was observed between increasing EDSS and worsening PRO scores, this is not an argument for relying on the EDSS as a measure of overall disease limitations and symptoms. The EDSS is primarily a physical impairment scale, heavily weighted toward motor function and ambulation, that provides limited or no information about other disease aspects such as pain, fatigue, cognitive impairment, and bladder problems. The association between worsening PROs and physician-derived EDSS score is simply further confirmation of the validity of PROs and does not imply any specific relationship between different symptoms and EDSS score.

We did not observe statistically significant differences in PROs in the CIS group stratified by EDSS at 5 years, but this analysis is limited by the small number of patients who experienced even mild-to-moderate residual impairment as measured by the EDSS 5 years after their initial demyelinating event. Therefore, clinicians cannot assume that individuals with a CIS are asymptomatic.

Clearly, further investigation is required to understand the differences in PROs between the CDMS and CIS groups. For instance, do PROs at 5 years predict future disability or the delayed development of CDMS after 5 years? The availability of the 10-year follow-up data from CHAMPIONS will help answer this and other questions.

A limitation of this study is that the MSQLI does not include a measure of depression, an important and common symptom throughout the disease course. The MCS

PracticePoints

- Individuals with MS who have low Expanded Disability Status Scale (EDSS) scores experience significantly lower quality of life than those who have a clinically isolated syndrome.
- Common symptoms that occur in this group of MS patients include reduced overall physical well-being, fatigue, pain, and difficulty with bladder control.
- At this early stage of the disease, these symptoms are not associated with lesions on T2-weighted magnetic resonance images.
- Patient-reported outcomes are distinct from common metrics of MS severity, including EDSS scores and magnetic resonance imaging findings, and should be assessed with equal concern.

of the SF-36 is included in the MSQLI. The dimensions it assesses include vitality, social functioning, role-emotional, and mental health. The last of these dimensions includes the following items: 1) Have you been a nervous person? 2) Have you felt so down in the dumps that nothing could cheer you up? 3) Have you felt calm and peaceful? 4) Have you felt downhearted and blue? and 5) Have you been a happy person? A trend was observed for the CDMS group to have lower mean (SD) scores (46.5 [10.2]) on the MCS than those who did not convert to CDMS (50.2 [9.4]) ($P > .001$ but $< .01$), suggesting that overall emotional well-being is lower in the CDMS group than in the non-CDMS group.

Although a major focus for many clinicians treating newly diagnosed patients is initiating disease-modifying therapy, the data from this study suggest that many symptoms negatively affect quality of life early in a person's disease course. It is therefore suggested that clinicians routinely monitor, educate, and treat patients for these symptoms from the time of diagnosis. These data indicate that clinicians should be particularly attentive to issues regarding their patients' overall sense of physical and mental well-being, perceptions of cognitive deficits, fatigue, pain, and bladder control.

Recommended resources for those interested in learning more about these symptoms of early MS and their management appear in a list of "Suggested Readings" at the end of this article. □

Financial Disclosures: This study was funded by a grant from Biogen Idec, Inc. The authors acknowledge editorial contributions to the manuscript by Sabrina Maurer, PharmD, and Matthew Hasson of Scientific Connexions. This support was funded by Biogen Idec. Dr. Miller has received consulting fees from Novartis. Dr. Kollman reports grant support from Biogen Idec to the Jaeb Center (2000–2008). Dr. O'Connor has received consulting fees from Biogen Idec, Bayer, Teva, Novartis, Sanofi Aventis, Genzyme, Roche, and Bristol Myers, and lecture fees from Bayer, Biogen Idec, Sanofi Aventis, and Teva. Dr. Kinkel has received consulting fees from Biogen Idec, Genentech, Novartis, and Teva, lecture fees from Biogen Idec and Teva, and grant support from Biogen Idec (1998–2008). Dr. Kalajian has nothing to disclose.

References

1. Brex PA, Ciccarelli O, O'Riordan JI, et al. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med*. 2002;346:158–164.
2. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol*. 2001;50:121–127. Comment in: *Ann Neurol*. 2006;59:871.
3. Adriaanse MC, Dekker JM, Spijkerman AMW, et al. Health-related quality of life in the first year following diagnosis of Type 2 diabetes: newly diagnosed patients in general practice compared with screening-detected patients. The Hoorn Screening Study. *Diabet Med*. 2004;21:1075–1081.
4. Elberling TV, Rasmussen AK, Feldt-Rasmussen U, Hording M, Perrild H, Waldemar G. Impaired health-related quality of life in Graves' disease: a prospective study. *Eur J Endocrinol*. 2004;151:549–555.
5. Weisscher N, Post B, de Haan RJ, Glas CAW, Speelman JD, Vermeulen M. The AMC Linear Disability Score in patients with newly diagnosed Parkinson disease. *Neurology*. 2007;69:2155–2161.
6. Nortvedt MW, Riise T. The use of quality of life measures in multiple sclerosis research. *Mult Scler*. 2003;9:63–72.
7. Gruenewald DA, Higginson IJ, Vivat B, Edmonds P, Burman RE. Quality of life measures for the palliative care of people severely affected by multiple sclerosis: a systematic review. *Mult Scler*. 2004;10:690–704.
8. World Health Organization. *International Classification of Impairments, Disabilities and Handicaps (ICIDH): A Manual for Classification*. Geneva: World Health Organization; 1980.
9. Kinkel RP, Kollman C, O'Connor P, et al. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. *Neurology*. 2006;66:678–684.
10. National Multiple Sclerosis Society, Consortium of Multiple Sclerosis Centers. *Multiple Sclerosis Quality of Life Inventory: A User's Manual*. New York: National Multiple Sclerosis Society; 1997.
11. Miller DM, Cohen JA, Kooijmans M, Tsao E, Cutter GA, Baier M. Change in clinician-assessed measures of multiple sclerosis and subject-reported quality of life: results from the IMPACT study. *Mult Scler*. 2006;12:180–186.
12. Dilonzo T, Halper J, Picone MA. Reliability and validity of the Multiple Sclerosis Quality of Life Inventory in older individuals. *Disabil Rehabil*. 2003;25:891–897.
13. Marrie RA, Miller DM, Chelune GJ, Cohen JA. Validity and reliability of the MSQLI in cognitively impaired patients with multiple sclerosis. *Mult Scler*. 2003;9:621–626.
14. Cohen JA, Cutter GR, Fischer JS, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology*. 2002;59:679–687.
15. Bethoux FB, Miller DM, Stough D. Efficacy of outpatient rehabilitation after exacerbations of multiple sclerosis. *Arch Phys Med Rehabil*. 2005;84:A10.

16. Ware JE Jr, Kosinski M, Bayliss MS, et al. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care*. 1995;33:AS264-AS279.
17. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the Fatigue Impact Scale. *Clin Infect Dis*. 1994;18(suppl 1):S79-S83.
18. Sherbourne CD, Stewart AL, Ware JE Jr. Pain measures. In: *Measuring Functioning and Well-being: The Medical Outcomes Study Approach*. Durham, NC: Duke University Press; 1992:220-234.
19. Nowinski JK, LoPiccolo J. Assessing sexual behavior in couples. *J Sex Marital Ther*. 1979;5:225-243.
20. Sullivan ML, Edgley K, Dehoux E. A survey of multiple sclerosis, I: perceived cognitive problems and compensatory strategy use. *Can J Rehabil*. 1990;4:99-105.
21. Sherbourne CD, Stewart AL. The MOS Social Support Survey. *Soc Sci Med*. 1991;32:472-480.
22. Veit CT, Ware J. The structure of emotional distress and well-being in general populations. *J Consult Clin Psychol*. 1999;51:730-732.
23. Kurtzke J. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444-1452.
24. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology*. 2003;61:1528-1532.
25. Ware JE, Kosinski M, Dewey JE. *How to Score Version 2 of the SF-36 Health Survey*. Lincoln, RI: QualityMetric; 2000.

Suggested Readings

- *Fatigue and Multiple Sclerosis: Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis*. Multiple Sclerosis Council for Clinical Practice Guidelines; 1998.
- *Urinary Dysfunction and Multiple Sclerosis: Evidence-Based Management Strategies*. Multiple Sclerosis Council for Clinical Practice Guidelines; 1999.
- Holland N, Halper J (eds). *Multiple Sclerosis: A Self-Care Guide to Wellness*. 2nd ed. New York: Demos Medical Publishing; 2005.
- Schapiro R. *Symptom Management in Multiple Sclerosis*. 5th ed. New York: Demos Medical Publishing; 2007.