A systematic approach to analyse health-related quality of life in multiple sclerosis: the GEDMA study

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Objective: To describe a holistic and comprehensive approach to the assessment of sufferer's perceptions of health-related quality of life (HRQoL) in a cohort of multiple sclerosis (MS) patients. *Methods:* The GEDMA (Grupo de Enfermedades Desmielinizantes de Madrid, in Spanish) study is an ongoing longitudinal survey using quantitative and qualitative methodologies. The baseline cohort consisted of a large sample of MS patients recruited from 13 hospitals in Madrid, Spain. Using a standardized protocol we collected data concerning the sociodemographic and health status characteristics of patients, as well as implementing a modified Spanish version of the Functional Assessment of Multiple Sclerosis quality of life instrument. Primary caregivers were interviewed using a specific protocol combined with the Zarit Burden Interview. *Results:* The index cohort comprised 371 MS patients (68.7% female) of mean age 38.9 ± 0.9 years. Age, sex and clinical form distribution were similar to other MS population-based surveys. There were 258 (69.5%) relapsing–remitting (RR) MS patients and 113 (30.5%) progressive MS patients. More than one-third of the married patients with progressive MS and almost a quarter of the RRMS patients separated or divorced following a diagnosis of MS; 71.3% of the progressive MS patients as well as 65.8% of the RRMS patients were unemployed as a consequence of the disease. Qualitative analysis showed that friendship and family relationships and occupational status were the most significant dimensions influenced by MS. On the other hand, the speech analysis of primary caregivers showed that emotional burden was related to patients' physical disability. Furthermore, primary caregivers described the influence of MS on their own occupational status, their nonacceptance of the disease, a perception of a lack of support by other members of the family as well as a 'selfish and intransigent' attitude of the patients themselves. *Conclusions:* The analysis of the GEDMA cohort provides valuable information that helps clarify the impact of MS on patients' HRQoL.
Multiple Sclerosis (2004) **10,** 47–54

Key words: health-related quality of life; multiple sclerosis; prospective study; qualitative methodology; quantitative survey

Introduction

Multiple sclerosis (MS) is one of the most common causes of chronic disability in young adults. The core symptoms of MS considerably impact upon the activities of daily living of patients. In addition, the disease has important psychological and, not infrequently, psychiatric consequences.[1] This combination means that MS affects the quality of life (QoL) experienced by patients and their families to a greater extent than several other chronic diseases.[2,3]

QoL is a term used in social science to refer to a subjective sense of wellbeing or global satisfaction with important aspects of life. In public health and medicine, the concept of health-related quality of life (HRQoL) refers to those aspects of life quality or function that are influenced by health status. This term is more specific than QoL and is based on health dimensions that can be measured. Tracking HRQoL in different populations can identify subgroups associated with particular physical or mental health complications, which may help guide policies or interventions to improve their health. As a result, assessment of HRQoL is increasingly becoming important for clinical research, clinical practice and service planning in health policy.[4–8]

The aim of this article is to describe a comprehensive methodological approach to the assessment of patients' perception of HRQoL: the GEDMA (Grupo de Enfermedades Desmielinizantes de Madrid, in Spanish) study.

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Methods

General study design
The GEDMA group was constituted in 1998 by a cohort of Spanish neurologists with expertise in MS. In 1999, a specific study regarding the HRQoL in a sample of MS

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patients and their primary caregivers was proposed: the GEDMA study. The baseline cohort consisted of a sample of MS patients from 13 Spanish hospitals in Madrid. MS patients were recruited by random sampling from MS databases in each hospital (see below for eligibility criteria of this study).[9–13] The GEDMA study began in 2000 and the MS cohort was followed over two years. Evaluations included changes in physical, psychological and social domains. The study was approved by the Móstoles General Hospital Research Ethics Board.

Eligibility criteria   The eligibility criteria were those used in a previous HRQoL survey of MS.[14] Patients, aged 18 and over, were included in the study if they had met the Poser committee diagnostic criteria for at least three months before inclusion and gave informed consent.[15] Patients excluded from the study were those a) institutionalized at the time of observation, b) those who had major acute comorbidities or any major serious chronic illness three months before inclusion (patients with a stable chronic medical condition were included), c) patients with any neurological illness other than MS, and d) those who had participated in any drug- or nondrug-related trials in the past three months.

Caregivers were selected for the study if they dedicated to the care of patients at least one hour a day.[16]

Quantitative methodology   Each patient gave his/her informed consent after the nature of the study and its procedure was fully explained by mail. The interviewer made an appointment by telephone to administer the protocol in the hospital setting or at home, depending on the patient's preference. Patients included in the baseline cohort were interviewed with a standardized questionnaire. The instruments were all administered face-to-face by a sociologist (JR-N) specialized in health sciences. When the patient was not capable of filling in the questionnaires because of physical problems, assistance was provided. This protocol was structured to include the following aspects (the main questionnaires are described below): a) social and demographic data; b) HRQoL measured with a modified Spanish version of the Functional Assessment of Multiple Sclerosis (FAMS) QoL instrument;[17,18] c) care needs or technical helps in the daily life as well as the existence of architectonic barriers at home and in the neighbourhood; d) the influence of the disease on educational or working activities; e) an examination of how distressing situations affect the disease process; f) attitudes of the family members towards the disease and how it affects the partner relationship; g) the use of alternative therapies; and h) emotional and cognitive functioning.

Caregivers were interviewed using a questionnaire covering social and demographic data, relationship with the patient, daily hours of care, care at night, influence of MS on the caregiver's occupational life, drugs for caregiver depression, and support received from other members of the family and/or formal caregivers. Lastly, caregiver burden measured with a Spanish adaptation of the Zarit Burden Interview (see later) was administered.[19,20]

Qualitative methodology   The qualitative methodology consisted of three focus groups composed of patients and another one composed of primary caregivers to discuss the needs and attitudes towards the disease. The focus groups were conducted at the same time as the structured interviews. Regarding the patient assessments, the main aspects that were analysed were the influences of the disease on the family (including marital aspects) and social networks (relatives, friends, and neighbors), the relationship between disease and working life, and their handicaps resulting from physical disabilities. Regarding family caregivers, we wanted to study in depth the understanding they had about the consequences of this disease upon other relatives as well as the conflicts the disease had caused within the different dimensions of life.

Clinical variables   The main clinical characteristics were obtained from review of well-documented neurological records. An Expanded Disability Status Scale (EDSS) score was assigned by each clinical neurologist.[21] Four clinical variables were used to form subgroups of MS patients: gender; EDSS score; disease duration; and clinical course. Three subgroups were formed according to EDSS score: a) low physical disability (EDSS 0–2.5); moderate physical disability (EDSS 3.0–5.5); and high physical disability (EDSS $\geq$ 6.0). Disease duration was defined as the period between the first symptom and the assessment day. For clinical course, two subgroups were defined: relapsing–remitting (RR) and progressive [secondary progressive (SP) or primary progressive (PP)].

Main questionnaires of the study protocol

HRQoL instrument   In its original version, the FAMS QoL instrument is an MS-specific HRQoL assessment that captures six main HRQoL domains: a) Mobility (seven items); b) Symptoms (seven items); c) Emotional Wellbeing (seven items); d) General Contentment (seven items); e) Thinking/Fatigue (nine items); and f) Family/Social Wellbeing (seven items).[17] An analysis of this modified FAMS version, applied in a sample of Spanish MS patients, showed slightly higher reliability if eight additional MS-specific items, which had been initially excluded from the original version, were now included.[18] In this survey, we applied both the original Spanish translated version of the FAMS QoL instrument as well as the modified version.

Cognitive functioning instruments   Study participants were administered a version of the Mini-Mental State Examination (MMSE). A few simple cultural modifications were necessary. 'State' was replaced by 'Country', and instead of being asked for the 'County', subjects were asked for the names of two main streets nearby. Apart from this, the test was carried out as described in the original version, 30 points being the highest possible result.[22] Furthermore, the clock drawing test (CDT) was also implemented. Clock drawings were administered with the command version; 10 points being the best possible result.[23]

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Emotional functioning instruments Depression symptoms were assessed with a Spanish version of the Hamilton Rating Scale for Depression (17-item version);[24] scores range from 0 to 52 points. Anxiety symptoms were assessed with a Spanish version of the Hamilton Rating Scale for Anxiety (14-item version);[25] scores range from 0 to 56 points. In both instruments, higher scores indicate higher levels of depression and anxiety, respectively.

Caregiver burden instrument Caregiver burden was assessed with the Zarit Burden Interview. This generic scale consists of 22 items that examine the impact of the care receiver's disabilities on the caregiver's emotional, social, physical and financial wellbeing.[19,20] The Burden Interview is scored by summing the responses to the individual items. The possible range is from 0 to 88. A higher score indicates a greater level of burden.

Results

Main characteristics of the GEDMA cohort

Of the 484 MS patients who were deemed eligible for the study, 371 persons (76.6%) were interviewed. The remaining 113 subjects were lost to the study because of address change (83, 73.4%), refusal (29, 25.6%) or death (one, 0.9%). There were no statistically significant differences in age groups ($\chi^2 = 5.407$, $P = 0.14$), sex ($\chi^2 = 2.138$, $P = 0.14$) and clinical course of MS ($\chi^2 = 4.525$, $P = 0.10$) between those subjects who participated in the study and those who did not participate. The index study cohort then composed of 371 MS patients (68.7% female), mean age 38.9 ± 0.9 years (range 18–74 years). Table 1 shows the age and sex distribution of this cohort. The age distribution was similar to other population-based cross-sectional surveys (Table 2). Table 3 shows the age and sex distribution of the GEDMA cohort according to the clinical course. This comprised 69.5% RRMS and 30.5% progressive MS of which 80 patients (21.6%) had SPMS. Figure 1 shows that the clinical distribution in the GEDMA cohort was not significantly different from other population-based cross-sectional surveys. Detailed clinical information defined by clinical course is shown in Table 4. Of the RRMS patients, 78.3% were fully ambulatory, while 89.4% of the progressive MS patients required aid for ambulation, with

more than 75% using canes, crutches or wheelchairs. Table 5 shows the mean scores on the FAMS QoL instrument version of the RRMS and the progressive MS patients. With regard to the psychosocial factors, Table 6 shows that more than one-third of the married patients with progressive MS and almost one-quarter of the RRMS patients separated or divorced because of the disease. Moreover, 71.3% of the progressive MS patients, as well as 65.8% of the RRMS patients, were unemployed as a consequence of the disease.

The main characteristics of the MS patients' caregivers of the GEDMA cohort have been recently published.[16]

Focus groups results

The main characteristics of the subjects that composed these groups are shown in Table 7. Open-ended questions were asked about areas of main concern to MS patients. Four sessions were carried out to allow discourses of both the patients and the primary caregivers. These were focused on different dimensions of family and occupational life.

The speech analysis of patients showed that friendship and family relationships as well as occupational domains were the most important dimensions influenced by MS. All patients who participated in the focus groups revealed that unemployment was a difficult issue. Strategies to minimize this problem included improving the economic conditions of the invalidity/incapacity benefit or facing the lack of job opportunities through participation in patients' organizations. On the other hand, the speech analysis of primary caregivers showed that emotional burden was related to patients' physical disability. Furthermore, primary caregivers described the influence of MS on their own occupational status, their nonacceptance of the disease, a perception of a lack of support by other members of the family, as well as a 'selfish and intransigent' attitude of the patients themselves.

Discussion

MS has major consequences on HRQoL among MS patients and their relatives.[26,27] However, contrary to physicians' beliefs, physical disability is not always the main determinant of overall HRQoL. Indeed, physicians

Table 1 Age and sex distribution of the GEDMA cohort

Age	Women		Men		Both sexes	
	No. of cases	%	No. of cases	%	No. of cases	%
≤ 24	17	6.7	9	7.8	26	7.0
25–29	37	14.5	13	11.2	50	13.5
30–34	52	20.4	18	15.5	70	18.9
35–39	46	18.0	16	13.8	62	16.7
40–44	39	15.3	19	16.4	58	15.6
45–49	30	11.8	13	11.2	43	11.6
50–54	16	6.3	13	11.2	29	7.8
≥ 55	18	7.1	15	12.9	33	8.9
Total	255	100.0	116	100.0	371	100.0

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Table 2 Age distribution of the GEDMA cohort compared with three Spanish prevalence studies of MS

	GEDMA, n = 371		Alcoy[a], n = 54		Teruel[b], n = 46		Móstoles[c], n = 85	
	n	%	n	%	n	%	n	%
≤ 29	76	20.5	17	20.0	10	21.7	8	14.8
30−44	190	51.2	45	52.9	19	41.2	24	44.4
45−54	72	19.4	16	18.8	10	21.7	15	27.8
≥ 55	33	8.9	7	8.2	7	15.2	7	13.0

[a] See reference number [7].
[b] See reference number [10].
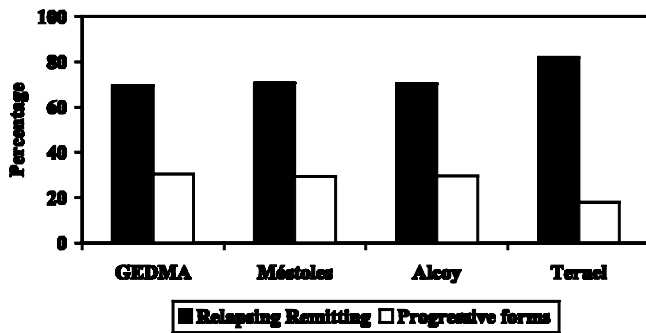[c] See reference number [11].

Figure 1 *Clinical forms distribution of the GEDMA cohort compared with three Spanish prevalence studies of MS.*

are more concerned than MS patients about the physical manifestations of disease. Patients themselves, identify vitality, role limitations caused by emotional problems, bodily pain and mental health as the most important determinants of their overall QoL.[28,29] Interestingly, MS may affect patient's HRQoL dramatically even in those with low EDSS scores and when impairment of mobility is not yet a major complaint.[30] That said, there is a relationship between HRQoL and clinical course. A recently published investigation demonstrated that a long duration of illness and high illness severity correlated with low HRQoL.[31] These findings are not necessarily contradictory, as certain complications of MS impact upon individuals early in the disease course, while others impact late. An analysis of the GEDMA cohort supported these findings.[32]

Emotional (depression and anxiety), cognitive and social status play an important role in patient's HRQoL.[30,32–36] Our assessments of cognitive, depressive and anxiety complications were graded by rating scales. Specifically, we decided to use the CDT and MMSE because both instruments have been recommended as a brief cognitive testing in MS.[37] Our aim was not to make a definitive clinical diagnosis of cognitive dysfunction or mood disorder but to assess the influence of neuropsychiatric symptoms on HRQoL. In our previous analysis of the GEDMA cohort, we showed that poor cognitive function and the high depressive and anxiety symptoms were associated with the low HRQoL scores.[32] In our view clinicians should supplement HRQoL measurement in MS patients with assessment of cognitive and emotional aspects. These frequently overlooked symptoms dramatically impact upon patient and caregiver wellbeing more than any other single dimension.[38] Once recognized, such

Table 3 Clinical form distribution of the GEDMA cohort by sex and age

Age groups by sex		Clinical forms				Total	
		RRMS		Progressive forms			
		No. of cases	%	No. of cases	%	No. of cases	%
≤ 24	Women	15	57.7	2	7.7	17	65.4
	Men	8	30.8	1	3.8	9	34.6
25−34	Women	75	62.5	14	11.7	89	74.2
	Men	25	20.8	6	5.0	31	25.8
35−44	Women	62	51.7	23	19.2	85	70.8
	Men	25	20.8	10	8.3	35	29.2
45−54	Women	27	37.5	19	26.4	46	63.9
	Men	10	13.9	16	22.2	26	36.1
≥ 55	Women	7	21.2	11	33.3	18	54.5
	Men	4	12.1	11	33.3	15	45.5
Total	Women	186	50.1	69	18.6	255	68.7
	Men	72	19.4	44	11.9	116	31.3

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Table 4 Clinical charateritics of the RR and the progressive MS patients

	RR		Progressive forms		Total	
	n = 258	%	n = 113	%	n = 371	%
EDSS score	2.44±1.6		6.31±1.3		3.62±2.3	
≤ 2.5	152	58.9	1	0.9	153	41.2
3−5.5	97	37.6	29	25.7	126	34.0
≥ 6.0	9	13.5	83	73.5	92	24.8
Disease duration (years)	9.4±6.3		12.9±8.1		10.2±7.1	
Aid for ambulation						
Fully ambulatory	202	78.3	12	10.6	214	57.7
Walking with aid of another person	25	9.7	12	10.6	37	10.0
Walking with aid of cane or crutches	26	10.1	41	36.3	67	18.1
Wheelchair bound	5	1.9	45	39.8	50	13.5
Bed bound	0	0	3	2.7	3	0.8
Mean age at onset (years)	27.2±8.9		32.0±11.5		28.7±10.0	

Table 5 Score on the FAMS quality of life instrument version of the RR and the progressive MS patients

	RR (n = 258)	Progressive forms (n = 113)
Mobility	19.2±6.7	8.0±6.0
Symptoms	39.0±10	34.43±8.5
Emotional wellbeing	21.7±6.0	15.9±7.6
General contentment	24.0±6.6	16.5±8.3
Thinking/fatigue	23.4±8.8	19.2±8.8
Family/social wellbeing	22.3±4.7	20.6±5.4
Total FAMS	149.6±35	114.6±32.3

Higher scores reflect better quality of life.

complications are treatable and this treatment has been shown to improve HRQoL.[39]

Despite great strides in this field, further longitudinal studies are essential in order to clarify the following questions. First, what is the relationship between individual complications of MS and HRQoL at each stage of the disease and in each disease subtype? Secondly, what are the modifying factors mediating disability and HRQoL (in particular the role of coping styles, social support and doctor−patient variables)? Thirdly, what is the effect of new drug treatments for MS on HRQoL, and how is this influence explained (for example, through functional, cognition, social or emotional benefits)?[40–43] All of these questions encouraged us to develop the GEDMA project.

Table 6 Psychosocial characteristics of the GEDMA cohort according to clinical course

	RR		Progressive forms		Total	
	No. of cases	%	No. of cases	%	No. of cases	%
Family sphere						
Married	143	55.4	19	69.9	222	59.8
MS affects couple relationship	45	17.4	40	35.4	85	22.9
Separated/divorced because of MS	11	24.4	15	37.5	26	30.6
Labour status						
Active/full-time employment	112	43.4	12	10.6	124	33.4
MS has negative repercussions on employment	71	63.4	12	100.0	41	33.1
Unemployed because of MS	96	65.8	72	71.3	168	68.0
Neighbourhood status						
Patients who refer the presence of architectonical barriers	101	39.1	79	69.9	180	48.5
Patients with troubles to get around in public places[a]	36	13.9	74	65.5	110	29.6
Family and social support[a]						
Patients who get emotional support from family	230	89.2	91	80.5	321	86.5
Patients whose family has accepted MS	215	83.3	84	73.3	299	80.6
Patients whose family has trouble understanding when MS gets worse	144	55.8	82	72.6	226	60.9
Patients who feel distant from friends	203	78.7	65	57.5	268	72.3
Patients who get support from friends and neighbours	200	77.5	66	58.4	266	71.7
Patients who feel 'left out' of things	18	7.0	15	13.3	33	8.9
Patients who have to limit social activity because of MS	59	22.9	77	68.1	136	33.6

[a] These items have been extracted from the FAMS QoL instrument.

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Table 7 Main characteristics of focus groups

	Focus groups with patients			Focus group with caregivers
	Group 1	Group 2	Group 3	Group 1
Sex				
Women	6	0	4	9
Men	0	6	4	1
Age				
≤ 24	0	1	0	1
25–29	1	0	2	1
30–34	0	0	1	0
35–39	1	2	2	3
40–44	3	2	3	1
45–49	0	0	0	0
≥ 50	1	1	0	4
MS course				
RR	4	3	4	–
Progressive forms	2	3	4	–
EDSS				
≤ 2.5	3	0	2	–
3–5.5	1	4	2	–
≥ 6	2	2	4	–
Relationship				
Wife	–	–	–	6
Mother	–	–	–	2
Father	–	–	–	1
Daughter	–	–	–	1

The main goal of our study was to obtain and define an MS cohort representing the entire clinical spectrum of the disease. To our knowledge, only six previous cross-sectional studies have obtained a representative sample of MS patients.[26,44–48] Unlike these studies, ours used a face-to-face interview, which facilitated an atmosphere of confidence for patients to discuss their problems and difficulties. An interviewer may also tailor an interview to suit a subject's particular life circumstances by explaining unclear terms or ideas. This is a particularly important consideration when working with a disease with a high prevalence of cognitive impairment, such as MS.

Any approach centred around the patient's perception of HRQoL may be enhanced by combining quantitative and qualitative methodologies. To date, only one published study has used both methodological approaches in MS.[34] However, unlike the current survey, they did not compare qualitative data with quantitative results. The analysis of our cohort will allow us to obtain qualitative information about the needs of MS patients and illness intrusiveness according to the statements of themselves and their primary caregivers. The qualitative design has been useful for the screening of social values that determine attitudes and behaviours towards the disease. This technique permits us to obtain information about the perception and affection of the disease in both the patients and their caregivers. Furthermore, our ongoing longitudinal study will allow us to obtain information about the issues of MS patients' caregivers. A preliminary analysis in 91 primary MS patients' caregivers of the GEDMA cohort showed that patients' HRQoL is strongly related to the burden of their caregivers.[16]

We used both the Spanish translation of the original FAMS QoL instrument as well as a modified version to assess the HRQoL in our sample of MS patients.[17,18] The original version of the FAMS is a very useful, disease-targeted, instrument to evaluate MS patients' HRQoL.[17,46] However, although the original version of the FAMS instrument includes the dimension of interest, its main limitation is that it is overly weighted toward assessment of psychosocial consequences.[45] In contrast, the Spanish modified version of the FAMS instrument has seven additional items concerning MS symptoms. In work to date it is a valid instrument that allows researchers to accurately measure the HRQoL concerns of MS patients.[18] We feel that the modified FAMS offers a more holistic assessment of neurological symptoms and psychosocial complaints associated with MS in line with published recommendations regarding specific HRQoL instruments.[49,50] We hope that analysis of the GEDMA cohort will help to improve our understanding of the way in which various facets of MS impact upon patients' HRQoL.

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