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ORIGINAL ARTICLE

Health-related quality of life in clinically isolated syndrome and risk of conversion to multiple sclerosis

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Abstract

Background and objectives A few studies have found that low scores on self-rated health and quality of life measures are associated with following worsening disability in multiple sclerosis (MS). We wanted to estimate the association between self-rated quality of life scores among patients with clinically isolated syndrome (CIS) and the risk of subsequent conversion to definite MS.

Methods One hundred sixty-two patients from the GERONIMUS cohort with a symptom or sign suggestive of MS and without a definite diagnosis of MS at the time of inclusion were asked to evaluate their health-related quality of life according to MSQoL-54 scale. They were clinically assessed and mood and depression scales were applied. The association between the scores of these scales and the risk of converting to definite MS during a 5-year follow-up was estimated using the Cox- proportional hazard regression model.

Results Quality of life at examination was significantly lower compared to those of an age- and sex-adjusted general Italian population. During the follow-up, 116 patients (72%) converted to definite MS. No significant predictive effects were found for the summary scales of MSQol-54 or other scales. The estimates did not change after adjusting for age, sex, BMI, education, MRI findings, Expanded Disability Status Scale (EDSS) score, and treatment at time of examination.

Conclusion Persons with CIS in this cohort reported reduced self-rated quality of life compared to the general population, but variation in these scores was not associated with subsequent conversion from CIS to clinical definite MS.

Keywords Clinically isolated syndrome (CIS) · Multiple sclerosis · Prognostic factors · Prospective study · Quality of life · Self-rated health

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Introduction

Multiple sclerosis (MS) presents a great and to a large extent unpredictable variation in disease development [1]. Factors associated with both disease progression and a rapid development of disability include socio-demographic features, early change in Kurtzke Expanded Disability Status Scale (EDSS) [2] score, number and type of relapses, type of the initial symptoms, MRI findings, evoked potentials, and cerebrospinal fluid profile [1]. Still, these factors explain only a small part of the large variation in prognosis. Evidence consistently indicated that patient's poor physical and mental health-related quality of life (QoL) is associated with a poorer prognosis [3–10].

Between 60 and 80% of patients with a first sign or symptom of the disease (clinically isolated syndrome—CIS) will later experience a second sign or symptom satisfying the definition of definite MS often confirmed by accompanying MRI findings [11]. This conversion from CIS to definite MS may be interpreted as a crucial step in the disease development, and the timing of this event might be predictive of future progression. We have previously shown that disease activity measured by MRI was a strong predictor for conversion among 168 patients with CIS enrolled at 19 centers in Northern Italy [11]. Coherently, with the literature on the role of QoL in predicting MS progression, the aim of the present study is to test whether health-related QoL, assessed at the time of the first clinically isolated event, is associated with the occurrence and timing of a second event and development of definite MS.

Material and methods

The study was part of an Italian multicenter study (G.E.Ro.N.I.Mu.S) including 13 out of 19 neurological units of the Emilia-Romagna region (covering about 2.5 million inhabitants) and three other neurological units (Novara, Verona, Chieti) [11, 12]. The study protocol was approved by the ethical committees of all participating centers. Patients gave written informed consent to be enrolled in the study.

The study involved initially 214 patients who had been referred to the participating neurological units with symptoms suggestive of multiple sclerosis (CIS) started no more than 6 months prior to the first visit (Fig. 1). A total of 37 patients were excluded due to insufficient data or lack of consent (n = 18), alternative diagnosis during screening phase (n = 12), or alternative diagnosis during follow-up phase (n = 7). We further excluded nine patients who had received a clearly stated diagnosis of MS at baseline. The included 168 patients were then followed for up to 5 years with yearly MRI scans and registration of new symptoms. A diagnosis of definite MS was based on the 2001 McDonald's criteria [13]. More details on the study population and design are described elsewhere [11].

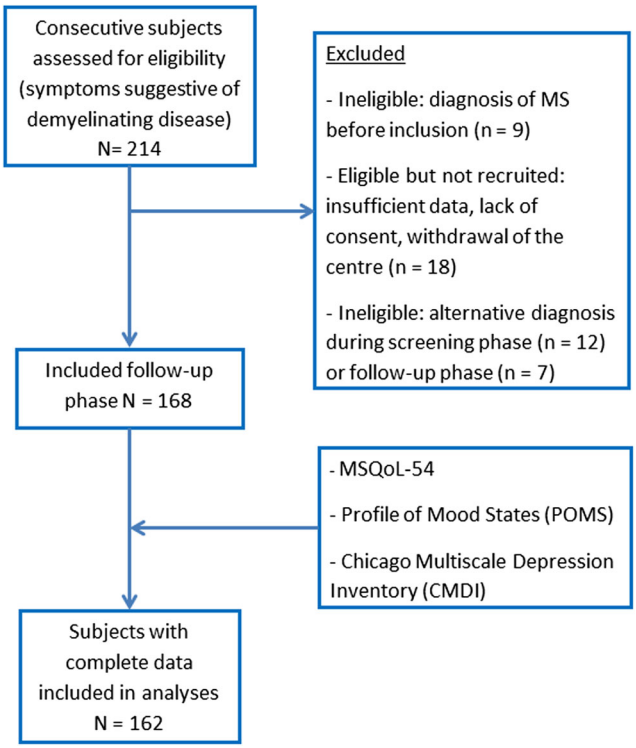

Fig. 1 GERONIMUS study flow diagram: eligibility, recruitment, and follow-up

Focusing on the previous 4 weeks, patients self-assessed their baseline health-related quality of life (HRQoL) through the Italian version of the MSQoL-54 questionnaire [14] consisting of the 36-Item Short Form Health Survey (SF-36) along with 18 additional MS specific items [15]. The MSQoL-54 is summarized in a physical and a mental summary scale, through a weighted sum of selected scales [15]. Conventionally, the SF-36 questions, which are included in the MSQoL-54 and are extracted in order to compare the study population with the age- and sex-adjusted general Italian population, are summarized in eight scales (physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, mental health) [16]. Higher scores indicate good health-related quality of life for all scales. The physical and a mental summary scale (categorized in quartiles) were used as the primary prognostic factors. We also compared the mean scores of the 8 SF-36 scales of the study population with the corresponding age- and sex-standardized scores of the general Italian population [17].

The study also included self-rated measures of (i) six distinct transient mood states (i.e., Tension or Anxiety, Anger or Hostility, Vigor or Activity, Fatigue or Inertia, Depression or Dejection, Confusion or Bewilderment) by means of the Profile of Mood States (POMS) scale [18] and (ii) three self-rated scales of depression (i.e., mood, depressive cognition, and vegetative symptoms) by means of the Chicago

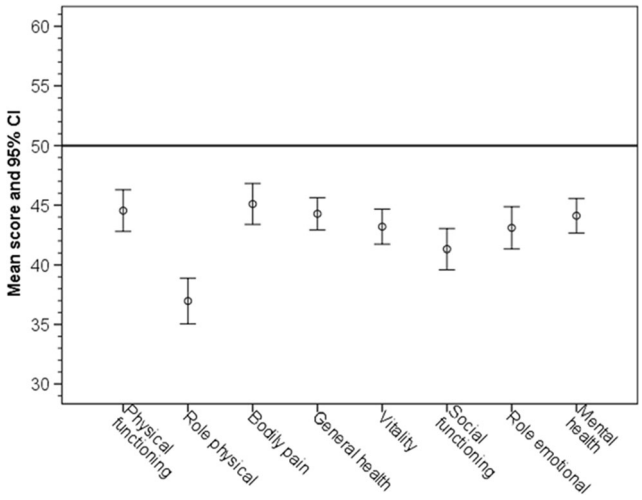

Fig. 2 Mean scores and 95% confidence interval of the standardized scores of the eight SF-36 scales for 162 patients in the GERONIMUS study. The general Italian population has a mean of 50 with a standard deviation of 10

Multiscale Depression Inventory (CMDI) [19]. The association between the predictors and the risk of conversion was estimated as hazard ratios (HR, 95% CI) using Cox proportional hazard regressions including possible confounding variables as covariates. The covariates included age at baseline (categorized as < 30 years of age, 30–39 years, and 40 years or more), sex, total MRI lesion load at baseline (categorized as 0, 1–5, 6–15, and 16 or more lesions), and EDSS score at baseline. We also made further correction for initiation of immune-modulating treatment at baseline, body mass index at baseline, and education. Those patients not having converted were censored at the end of the follow-up.

The effect of the physical and mental MSQoL-54 summary scores was estimated by categorizing the scores in quartiles and by adding a test for trend performed by using the categorical variable as a continuous variable. The proportional hazard assumption was checked for each covariate by visual inspection of the log minus log plots. No major deviation from this assumption was found.

The data analysis was performed by SPSS version 21.0 and STATA version 14.

Results

Out of 168 patients included, 162 were registered with complete scores on the MSQoL-54 at baseline. Mean age was 33.4 years and 68% were female patients.

The patients had markedly lower scores at disease onset on all the eight SF-36 scales compared to the sex- and age-adjusted general Italian population [17]. A reduction between 0.5 and 1 SD for all scales, except for "Role limitations due to physical problems" that was 1.3 SD lower, was observed (Fig. 2).

The follow-up time (from baseline to conversion or to the end of follow-up) ranged from 0.3 to 72.8 months with a median of 15.7 months IQR 7.3–36.1 (1.3 years, IQR 0.6–3.0). At the end of the 5-year follow-up, a total of 116 patients (72%) had converted to definite MS. The median time to conversion was 19.60 months (95% CI = 14.5–25.2) (Fig. 3).

We found no effect of either the physical and mental MSQoL-54 summary scales on the hazard of conversion to definite MS, even after adjustment for sex, age, total MRI lesion load, and EDSS score at baseline (Table 1). A test for trend was not significant for any of the two summary scales. Further adjustments for BMI, immune-

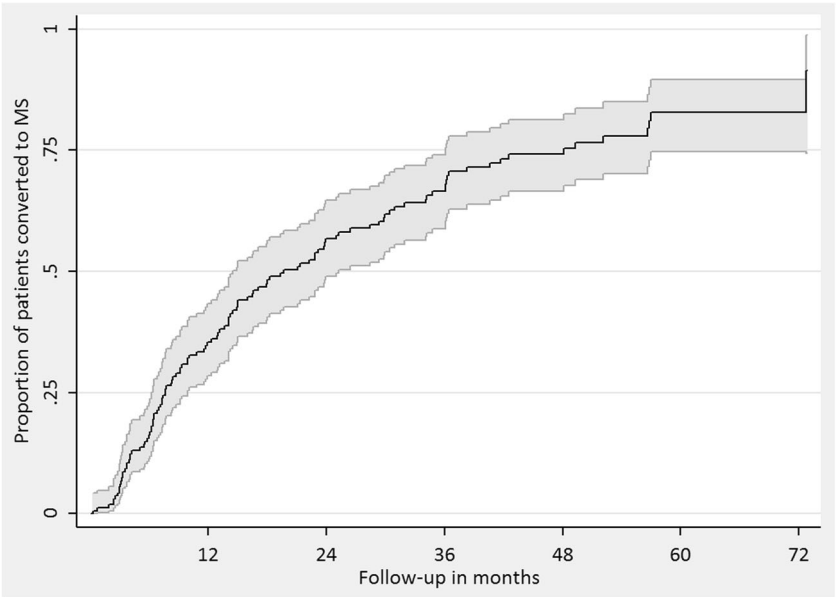

Fig. 3 Cumulative proportion (95% CI) of participants with CIS ($N = 162$) converted to definite MS during follow-up

Table 1 The physical and mental summary scores as predictors of conversion from CIS to definite MS among 162 patients in the GERONIMUS study. Hazard ratios with 95% confidence intervals estimated from univariate and multivariate Cox proportional hazard regression model

	Univariate analysis			Multivariate model		
Variable	HR[1]	95% CI	*p* value[2]	HR[1]	95% CI	*p* value[2]
Physical summary scale			0.66			0.52
Q4 highest scores	1			1		
Q3	1.07	0.63–1.83		0.80	0.42–1.50	
Q2	1.14	0.67–1.93		0.67	0.34–1.36	
Q1 lowest scores	0.83	0.50–1.39		0.49	0.21–1.13	
Mental summary scale			0.77			0.54
Q4 highest scores	1			1		
Q3	1.14	0.69–1.91		1.27	0.66–2.43	
Q2	0.85	0.50–1.46		1.00	0.52–1.93	
Q1 lowest scores	1.07	0.65–1.76		1.72	0.81–3.64	
Sex			0.06			0.59
Men	1			1		
Women	1.48	0.99–2.23		1.16	0.71–1.88	
Age at baseline			0.10			0.063
< 30 years	1			1		
30–39 years	0.81	0.54–1.22		0.67	0.42–1.08	
≥ 40 years	0.59	0.36–0.96		0.49	0.27–0.89	
Total number of MRI lesions at baseline			< 0.0001			< 0.0001
0	1			1		
1–5	4.74	1.13–19.9		4.06	0.93–17.68	
6–15	8.55	2.07–35.3		8.66	2.08–36.08	
≥ 16	12.9	3.10–53.5		14.04	3.30–59.64	
EDSS score at baseline			0.20			0.52
0	1			1		
1	1.13	0.68–1.90		1.34	0.76–2.37	
1.5–2	1.59	0.97–2.59		1.65	0.94–2.88	
> 2	1.00	0.56–1.77		1.19	0.59–2.37	

[1] Hazard ratio

[2] Overall *p* value for categorical variable

modulating treatment during follow-up and education did not change the results (data not shown).

We further tested each of the 12 subscales of MSQoL-54, the six scales of POMS and the summary score of CMDI; none of these factors was associated with time to conversion (data not shown).

Discussion

The variation in physical and mental quality of life in CIS patients early after clinical onset, is not associated with the time to conversion to a diagnosis of definite MS as defined according to 2001 McDonald's criteria [13]. This result has been found regardless the markedly lower scores reported by the study patients on all the eight SF-36 scales compared to the general Italian population.

We also considered the possible effect of psychological well-being given their possible role on QoL [20]. Consistently, with previous longitudinal evaluation on participants with CIS [21], there was no relationship between conversion to MS and patients' anxiety, hostility, or depression, assessed through POMS and CMDI.

Contrary to the literature that shows a prognostic effect of MS patients' quality of life scores in disease progression, the present findings indicate that baseline QoL in patients with CIS is not predictive of conversion to MS.

The divergent results could be due to methodological differences related to the study design, populations, and time intervals. For example, previous studies [3, 4, 6, 8] on patients with established diagnosis of MS used EDSS change over time as prognostic outcome. In the present work, conversion to MS is the target, and the diagnosis of MS in participants with CIS does not necessarily correspond to a change in EDSS. It is important to consider

also that our study population is rather homogeneous with regard to disease severity, patients were very early in the disease course with little variation in EDSS score, and more than 70% of the patients converted to definite MS with a median time of 13 months [3, 4, 6, 8].

Of note, we found that patients reported scores of the SF-36 were significantly lower compared to the general population. The patients reported a particularly lower score for the role limitations due to physical health problems, reflecting a marked influence of their disease on work and daily life. Interestingly, this scale showed a predictive effect in three of the previous MS prognostic studies [4, 6, 8].

Taking into account that our study has a relatively low power, reflected also by the wide confidence intervals, the negative results cannot rule out the possibility of an association between self-reported health-related QoL in patients with CIS and conversion to MS.

However, this finding, or these null findings, could be particularly relevant for future studies or meta-analysis with similar purposes.

Conclusions

In conclusion, the data from these 162 patients with CIS showed that the self-perceived quality of life is markedly reduced already at this early stage of the disease. Nevertheless, variation in these scales seems to be not associated with timing and occurrence of conversion to a definite MS diagnosis.

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Compliance with ethical standards

Conflicts of interest A. Gajofatto reports personal fees and grants from MERCK, non-financial support from NOVARTIS. F. Granella reports grants, personal fees, and non-financial support from Biogen, personal fees and non-financial support from Sanofi Genzyme, Novartis, Merck, and non-financial support from Almirall. M. Leone reports grants from TEVA. A. Lugaresi reports grants and personal fees from Bayer, Biogen, Merck, Novartis, Sanofi- Genzyme, Teva, and Almirall. S. Malagù reports non-financial support from Biogen, Sanofy-Aventis, personal fees and non-financial support from Merck-Serono, personal fees from Bayer, Novartis. E. Baldin, R. D'Alessandro, K. Mattarozzi, L. Motti, W. Neri, I. Pesci, T. Riise, M. Santangelo, C. Scandellari, M.R. Tola, L. Vignatelli, and C. Zenesini have no conflicts of interest to disclose.

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