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Anxiety, depression and impaired health-related quality of life are therapeutic challenges in patients with multiple sclerosis

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Abstract

Anxiety, depression and impaired health-related quality of life (HRQoL) are commonly reported in patients with multiple sclerosis (MS) and are of great interest for therapeutic approaches. Based on regional differences a quantitative assessment of these factors in comparison to the general population, and the consideration of demographic cofactors, would be useful when designing specific interventions. We adopted such an approach in a German cohort of MS patients. Anxiety, depression (HADS) and HRQoL (SF-36) were measured in 49 consecutive outpatients with MS and compared to age- and gender-adjusted control groups (n=1330 for HADS; n=5087 for SF-36) extracted from German National Health Surveys. Patients with MS showed significantly increased levels of anxiety and depression as well as decreased HRQoL with the exception of mental health; the effect sizes ranged from 0.39 (depression) to 1.06 (physical functioning). As could be expected, MS patients with relapsing-remitting clinical course had better physical functioning than patients with secondary progressive MS. There were strong relations between anxiety and depression (r=0.54; P<0.01), and between neurological impairment (EDSS) and physical functioning (r=-0.80; P<0.001) as well as depression (r=0.48; P<0.05). This investigation of MS patients confirms the prevalence and impact of anxiety, depression and most of the HRQoL dimensions in MS patients and provides evidence for the usefulness of a quantitative comparison to a region-specific general population as a starting point for therapeutic approaches.

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system that typically begins in early adulthood and often leads to long-term disability.[1] Due to the unpredictable course and extent of neurological symptoms, MS patients feel unexpectedly vulnerable fearing physical impairment during the disease course; therefore, the time of diagnosis often marks the beginning of various psychological reactions.[2] Depression and anxiety are the most commonly occurring complaints and the most frequently investigated aspects.[2,3] The origin of depression has been described as multi-factorial with genetic, inflammatory-immunological and psychological factors.[3] In contrast, anxiety is primarily assumed to be reactive.[3] Several studies have investigated the prevalence of major depression in MS patients and found a lifetime prevalence of about 50% and a 12-month prevalence of 25.7%.[2,4,5] For anxiety, studies report a lifetime prevalence of 35.7% for any anxiety disorder in consecutive MS patients,[6] and disproportionately high levels of anxiety around 34% in recently diagnosed patients with MS.[3,7] The investigation of mood disorders in MS patients may be hampered by the high co-morbidity of depression and anxiety.[3,5] In general, it is well-established that anxiety and depression in MS lead to disability, suffering and disruption of work, and social life; therefore, a specific screening of anxiety and depression is essential to provide treatment as soon as possible.[3]

In addition to this psychological perspective, it is recognized that long-term consequences of MS affect social and occupational issues, which may be independent of the problems caused by physical disability alone.[8] Health-related quality of life (HRQoL) can be considered as a multidimensional index of well-being that involves the individual patient's perspective.[8-10] Previous studies have assessed HRQoL in MS patients in comparison to the general population, which have resulted in inconsistent reports. For example, one study found worse scores for physical functioning, vitality and general health in a cohort of 185 MS patients in the US, but also domains that were similar to the general population.[11] In contrast, another study revealed lower scores in all HRQoL dimensions in 381 Australian MS patients compared to 291 people from the general population.[12] Equivalent reports exist for Italian,[13] Norwegian,[14] Canadian,[15] and German MS patients.[16] A further study has investigated HRQoL in different countries (France, Germany and UK) for regional comparison and found that physical functioning and general wellbeing were mostly affected when compared to patients without MS.[17] Moreover, this study reports on an inconsistent relationship between social function as one dimension of HRQoL and disease severity. These findings imply regional differences in self-assessed HRQoL in patients with MS, which might be caused by varying environment characteristics including health care logistics and social support.

Awareness of individual affected HRQoL dimensions and coincidental anxiety and depression is of great importance to design individual adapted therapeutic strategies in patients with MS. A quantitative assessment with a comparison to the national general population would, therefore, be preferable. Unfortunately, most previous studies have used qualitative analysis and report on percentages for clinically significant depression or anxiety, or have analyzed HRQoL domains as single factors. The present study therefore aims: i) to quantify differences between a German cohort of MS patients and the general population regarding anxiety, depression and HRQoL; ii) to explore the impact of age, gender, severity of neurological impairment and MS subtype; iii) to evaluate the relationship between these variables.

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Materials and Methods

In 2007, unselected consecutive outpatients attending the Department of Neurology of the University of Leipzig with an established diagnosis of MS were asked to participate in a survey using a standardized paper-and-pencil questionnaire. Data of 49 patients (all of them native Germans) were suitable for evaluation. Patients' characteristics are shown in Table 1.

The *severity of the neurological impairment* due to MS was quantified by the Expanded Disability Status Scale (EDSS).[18] The patients' mean EDSS was 3.3±2.4. For some analyses, patients were divided into two predefined groups: EDSS 0 to 4.5 (n=33; 67.3%) and EDSS 5.0 to 9.5 (n=16; 32.7%).

Anxiety and depression were measured with the German version of the Hospital Anxiety and Depression Scale (HADS).[19] In this questionnaire, a total of 14 items are scaled from 0 to 3 with item-dependent choices, of which 7 items each reflect the dimensions anxiety or depression, respectively. Higher values represent high intensity of each dimension. To assess *HRQoL*, the SF-36 questionnaire with a time window of four weeks was used.[20] A total of 36 items with item-dependent choices, partially scaled from 1 to 6, results in scores for 8 dimensions: physical functioning, role-physical functioning, bodily pain, general health, vitality, social functioning, role-emotional functioning, and mental health. For the SF-36, higher values imply better quality of life. Forms of both HADS and SF-36 were delivered by Hogrefe Testzentrale, 37027 Göttingen, Germany.

The first control group (HADS) was taken from a survey of the general German population[21] conducted in 1998. The second control group (SF-36) was derived from the German National Health Survey[22] conducted in 1997. Both samples are representative of German people living in private households. Since the mean ages and gender distributions of these surveys differed from the sample of the MS patients, age- and gender-adjusted control groups were derived by restricting to sub-samples with nearly equal distributions. This procedure yielded a HADS control group of 1,330 subjects (mean age 40.9±14.1 years; 27.4% males) and a SF-36 control group of 5,087 subjects (mean age 41.6±16.0 years; 27.8% males).

Statistical analyses

Questionnaire scores were used as rounded means with a tolerance of one missing item per scale for HADS and for SF-36, respectively. Descriptive statistics were applied for sample description. For differences between groups, the t-test for independent samples was used for two groups, or ANOVA for more than two groups; ANOVA was followed by the Duncan-test for comparisons of multiple mean values. To evaluate the degree of significant differences, effect sizes (Cohen's d) were calculated. Relations between variables were analyzed by linear regression or Pearson's correlations, respectively. Calculations were performed with SPSS (version 11.0).

Results

Figure 1 shows anxiety and depression in MS patients and the German general population. MS patients had significantly higher scores of anxiety and depression. The effect size is 0.61 for anxiety and 0.39 for depression. Figure 2 illustrates all 8 dimensions of the HRQoL in MS patients compared to the general population. In summary, patients with MS had significantly decreased quality of life with the exception of mental health. The effect sizes vary between 0.43 (role-emotional functioning) and 1.06 (physical functioning).

Table 2 gives an overview of the relationship between the measured dimensions and age, displayed as regression coefficients. Patients with MS showed significant relations exclusively in depression and physical functioning. According to this analysis, MS patients had

Table 1. Patients' characteristics.

Age in years [M (s.d.) range]	41.7 (10.6) 21-69
Gender	
Male [N (%)]	12 (24.5)
Female [N (%)]	37 (75.5)
Disease duration in years [M (s.d.) range]	8.0 (7.3) 1-16
Clinical course of MS	
Relapsing remitting (RR) [N (%)]	32 (65.3)
Secondary progressive (SP) [N (%)]	9 (18.4)
Primary progressive (PP) [N (%)]	6 (12.2)
Clinically isolated syndrome of CNS demyelination (CIS) [N (%)]	2 (4.1)*

M: mean; s.d.: standard deviation; *due to the small number, these patients were not used as a separate group in analyses of differences according to clinical course.

Table 2. Impact of age on anxiety, depression, and health-related quality of life in patients with MS compared to the general population (linear regression model with age as independent, and anxiety, depression and quality of life as dependent factors).

	Patients with multiple sclerosis		General population	
	Beta	P	Beta	P
Anxiety	-0.07	n.s.	0.16	***
Depression	0.36	*	0.32	***
Physical functioning	-0.53	***	-0.47	***
Role-physical functioning	-0.26	n.s.	-0.27	***
Bodily pain	-0.22	n.s.	-0.23	***
General health	-0.28	n.s.	-0.30	***
Vitality	-0.18	n.s.	-0.05	***
Social functioning	0.10	n.s.	-0.10	***
Role-emotional functioning	0.06	n.s.	-0.12	***
Mental health	-0.14	n.s.	-0.08	***

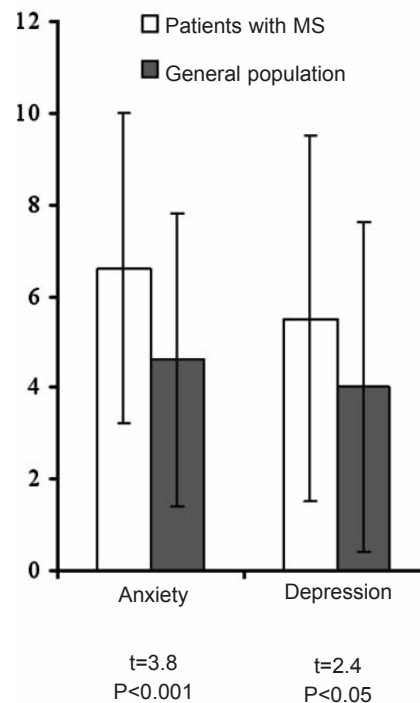Beta: Standardized regression coefficients; *P<0.05; ***P<0.001.

Figure 1. Anxiety and depression in patients with MS compared to the general population. Means are shown as bars and standard deviations as lines. T-values based on the t-test for unpaired samples.

Table 3. Anxiety, depression and health-related quality of life in patients with multiple sclerosis depending on EDSS and MS subtype.

| | EDSS | | | MS subtype | | | | |
	0 to 4.5 M (s.d.)	5 to 9.5 M (s.d.)	t-test t (P)	RR (I) M (s.d.)	SP (II) M (s.d.)	PP (III) M (s.d.)	ANOVA F (P)	DUNCAN (P<0.05)
Anxiety	7.1 (3.4)	5.5 (3.4)	1.5 (n.s.)	6.6 (3.4)	5.8 (3.6)	6.8 (4.0)	0.4 (n.s.)	n.s.
Depression	4.6 (3.4)	7.2 (4.6)	-1.9 (n.s.)	4.7 (3.1)	7.6 (5.3)	6.8 (4.0)	2.1 (n.s.)	n.s.
Physical functioning	71.3 (30.5)	15.4 (22.6)	6.9 (***)	67.4 (30.8)	11.9 (22.5)	30.0 (28.9)	9.9 (***)	I > II
Role-physical functioning	57.6 (40.7)	44.2 (39.7)	1.0 (n.s.)	4.8 (40.5)	57.1 (45.0)	29.2 (29.2)	1.7 (n.s.)	n.s.
Bodily pain	62.6 (30.9)	49.8 (28.0)	1.4 (n.s.)	57.3 (29.9)	48.1 (32.6)	65.4 (23.9)	1.8 (n.s.)	n.s.
General health	51.4 (22.1)	44.0 (22.5)	1.0 (n.s.)	49.2 (21.5)	46.8 (22.8)	39.8 (20.7)	2.1 (n.s.)	n.s.
Vitality	46.9 (21.3)	39.7 (23.9)	1.0 (n.s.)	44.4 (21.0)	41.9 (20.2)	29.2 (29.6)	1.5 (n.s.)	n.s.
Social functioning	72.3 (27.0)	75.0 (31.0)	-0.3 (n.s.)	71.9 (27.7)	76.6 (35.6)	70.8 (25.8)	0.2 (n.s.)	n.s.
Role-emotional functioning	69.8 (40.0)	88.9 (29.6)	-1.7 (n.s.)	71.3 (39.6)	85.7 (37.8)	77.8 (40.4)	0.3 (n.s.)	n.s.
Mental health	66.6 (17.3)	69.8 (22.4)	-0.5 (n.s.)	68.1 (13.1)	67.9 (24.6)	83.3 (28.0)	0.1 (n.s.)	n.s.

RR: relapsing remitting multiple sclerosis; SP: secondary progressive multiple sclerosis; PP: primary progressive multiple sclerosis; M: mean; s.d.: standard deviation; ***P<0.001.

Table 4. Correlation matrix of anxiety, depression, health-related quality of life and clinical characteristics in patients with multiple sclerosis.

	ANX	DEP	P	RP	B	G	V	S	RE	M	DIS	DUR
Anxiety (ANX)	-	0.54***	-0.08	-0.29	-0.20	-0.26	-0.45	-0.52***	-0.35*	-0.71***	-0.12	0.00
Depression (DEP)		-	-0.58***	-0.72***	-0.43**	-0.60***	-0.67***	-0.54***	-0.48**	-0.76***	0.48*	0.33*
Physical functioning (P)			-	0.57***	0.49**	0.48**	0.57***	0.31*	0.16	0.29	-0.80***	-0.51***
Role-physical functioning (RP)				-	0.50***	0.60***	0.67***	0.38**	0.43**	0.51***	-0.36*	-0.48**
Bodily pain (B)					-	0.55***	0.52***	0.32*	0.18	0.28	-0.28	-0.39**
General health (G)						-	0.66***	0.32*	0.24	0.42**	-0.26	-0.40**
Vitality (V)							-	0.58***	0.40**	0.67***	-0.24	-0.46**
Social functioning (S)								-	0.37*	0.54***	0.01	-0.17
Role-emotional functioning (RE)									-	0.63***	0.03	-0.01
Mental health (M)										-	-0.02	-0.17
Disability (EDSS: DIS)											-	0.55***
Duration of MS (DUR)												-

*P<0.05; **P<0.01; ***P<0.001.

increasing depression and decreasing physical functioning with increasing age. In contrast, the general population shows increasing anxiety and depression as well as decreasing HRQoL in all 8 dimensions with increasing age.

To test the impact of gender on anxiety, depression and HRQoL, t-tests were performed. In summary, male and female patients with MS did not differ significantly in any of the ten variables. This is again in contrast to the general German population, where women have higher scores for anxiety (P<0.001) and depression (P<0.001), as well as lower HRQoL in all 8 dimensions (P<0.001 for each).

Table 3 shows the impact of the severity of neurological impairment (EDSS) and of MS subtype. MS patients with more severe impairment report reduced physical functioning. For anxiety, depression and the other 7 dimensions of HRQoL, no significant relations were found. Similarly, as to MS subtype, only physical functioning as one of the HRQoL dimensions differs significantly among groups (ANOVA, Table 3). According to the *post hoc* Duncan-test, patients with a relapsing remitting course have a better physical functioning
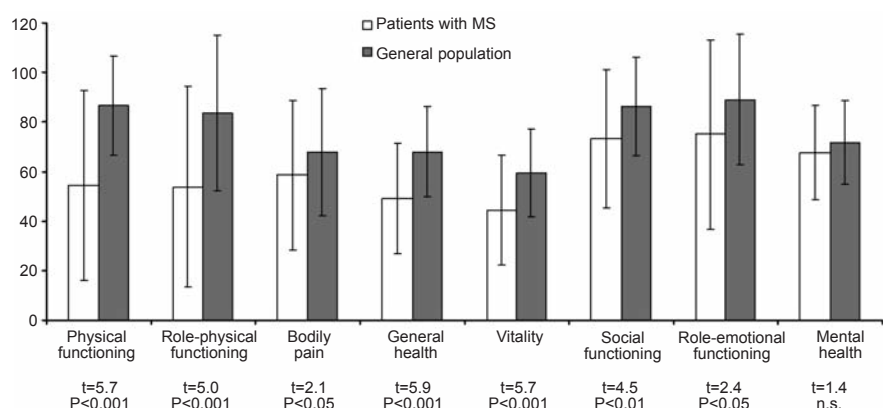

Figure 2. Health-related quality of life in patients with MS compared to the general population. Means are shown as bars and standard deviations as lines. T-values based on the t-test for unpaired samples.

than patients with secondary progressive MS.

All the recorded variables were analyzed in a correlation matrix (Table 4). Anxiety was significantly correlated to depression. Further, higher values of depression are correlated with lower HRQoL in all dimensions, while anxiety

is related to lower levels on the dimensions social functioning, role-emotional functioning and mainly mental health. All the coefficients between the 8 dimensions of the HRQoL questionnaire have positive algebraic signs; most of them are significant relations. Therefore,

increased levels of one aspect of quality of life are related to increased levels for most of the other fields of HRQoL. In addition, the correlation matrix shows a strong correlation of disease duration with depression and most aspects of HRQoL, and with neurological impairment. In contrast, anxiety does not correlate with duration of MS, and neurological disability alone was related to only some aspects of HRQoL.

Discussion

Comparison of multiple sclerosis patients to the general population

The present study demonstrates significantly increased levels of anxiety and depression as well as significantly impaired HRQoL in German MS patients in comparison to large, representative samples of the general German population. So far, anxiety and depression in MS have been analyzed using scales and cut-off values derived from the respective validation sample, or in case-control studies. Predominantly, studies have found an increased prevalence in patients with MS.[2,3] However, a comparison to rates in the general German population has not been reported. In the present study, quantitative analysis using effect sizes revealed the greatest differences in the dimensions anxiety, physical functioning, role-physical functioning and general health. This finding underscores the importance of psychological,[3] social and impairment-related aspects,[8,10] and their interrelation in patients with MS.[7,23,24] With respect to a few HRQoL dimensions, our data confirm results from other countries, but also deliver a specific pattern of impaired HRQoL. In detail, mental health was the only dimension that was not affected in our cohort of MS patients. In contrast, studies, that have assessed HRQoL out of Germany in a comparable modality, found predominantly impaired HRQoL in all 8 dimensions (Australia,[12] Italy,[13] Norway,[14] and Canada[15]). This finding confirms the usefulness of a region-specific analysis when designing treatment strategies in MS. Surprisingly, a previous German study reported on reduced HRQoL in all 8 dimensions of the SF-36 in MS patients,[16] but indicates no levels of significance or quantitative differences.

There are two major limitations to the present study. First, the number of patients is comparatively small. This is balanced by the fact that our present sample is demographically similar to the German MS registry (n=3223; 72% women; mean age 42.9±11.2 years)[16] suggesting that it could be considered representative. Second, the control groups were extracted from datasets acquired several years prior to the paper-and-pencil questionnaires in the patient sample. However, the differences were larger than could be reasonably expected to occur from spontaneous fluctuations or cultural drifts alone.

In addition to confirming impairments in the MS sample, our dataset allows for further detailed comparisons. In the general population, depression, anxiety and all domains of HRQoL are related to age. In contrast, this only applies to depression and physical functioning in MS patients. This interrelation is plausible in MS, and confirmed by positive correlations in our sample. Older age generally implies a longer disease duration, and consequently increased physical impairment. Physical impairment itself is a well-known aspect in the multi-factorial setting that generates depression.[3,23] Furthermore, it is remarkable that anxiety, depression and HRQoL depend less on gender than in the general population. Due to the small number of patients compared to the large control groups, however, this result must be interpreted with caution. One hypothetical explanation might be that more successful coping strategies employed by healthy men are less available to male MS patients. Studies in MS patients have investigated coping,[3,25] but mostly do not provide data separated by gender. Only one study aimed at coping strategies in connection with HRQoL and found that women use more diversion and palliative strategies than men.[26] Based on this fact, it could be postulated, that women with MS used diversion as coping with positive effects on HRQoL, thus the lack of gender-related differences in MS patients could be explained. Furthermore, this study provided evidence for the impact of MS subtype on HRQoL, especially physical functioning. Health care professionals should be aware of this, particulary in MS patients with secondary progressive disease course because of their greatly reduced physical functioning.

Depression, anxiety and HRQoL within the MS sample

The strong correlation between anxiety and depression (0.54) confirms the high co-morbidity of these psychological aspects, as described in previous studies.[3,5] The significant relationship between the EDSS and depression underlines the strong interrelation of physical impairments and emotional symptoms that has also been shown in previous studies.[25,27] In this respect, one earlier study found that anxiety and depression are intermediate factors, strengthening the effects of this relation between impairment (EDSS) and health-related quality of life (SF-36).[24] Together, these data strongly argue for awareness of depression in MS clinical care, especially since depression is usually a treatable disorder. It is important to point out, however, that depression is not necessarily a psychological consequence of MS, but also a symptom of the disease, sometimes attributable to specifically located brain lesions.[1,28] Interestingly, such attribution to regional abnormalities was not found for anxiety.[29] The significant negative correlation between physical functioning and EDSS confirms that increasing bodily impairment due to MS influences the subjective perceived HRQoL, primarily with regard to the physical dimension.[13,27,30] In studies using explicitly the SF-36, correlation coefficients have been obtained between physical functioning as one dimension of HRQoL and EDSS, for example -0.86,[14] or -0.73.[24] This compares favorably to the coefficient of -0.80 in our sample. This observation is in line with clinical experience and a study which showed that EDSS correlates significantly to physical functioning, but did not correlate with mental components of HRQoL.[31] Contrary to this, however, a Canadian study in 198 patients additionally found decreased social functioning according to EDSS step.[15]

In summary, self-reported depression and anxiety are more prevalent in German MS patients and depend less on age and gender than in the general German population. HRQoL is significantly lower than in the general population with the exception of mental health. These findings provide evidence for the usefulness of region-specific control groups while designing rehabilitation strategies. Furthermore, the interrelation of these variables hints to causal relationships, which offer therapeutic options and should be further studied longitudinally.

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