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Fatigue and depression predict health-related quality of life in patients with pediatric-onset multiple sclerosis

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ABSTRACT

Background: Fatigue, depression and loss in health-related quality of life (HRQoL) have been reported to occur in a substantial amount of patients with pediatric-onset MS (POMS). This study aims to evaluate depression, fatigue and HRQoL and its relationship in a cohort of patients with POMS and matched healthy controls (HCs).

Methods: In a multicenter cross-sectional study, Beck Depression Inventory II, Depressionstest für Kinder, the Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scale and the PedsQL™ Multidimensional Fatique Scale were performed.

Results: In a cohort of 106 patients with POMS and 210 matched HCs, patients were significantly more often depressed (21.7% vs. 11.4%, $p = 0.014$) experienced greater fatigue (40.6% vs. 17.3%, $p < 0.001$) and a greater loss of HRQoL (43.4% vs. 15%, $p < 0.001$) than controls. Depression predicted 51.8% of variance of fatigue. Fatigue was also predicted by female gender. Loss of HRQoL was predicted by EDSS, depression and fatigue. Depression and fatigue together explained 67.7% of variance of HRQoL.

Conclusion: Patients with POMS are at a significant increased risk for depression, fatigue and loss of HRQoL. Furthermore, fatigue and depression significantly predict reduced HRQoL in POMS, suggesting that testing for these symptoms and early therapy is of utmost importance in all patients with POMS.

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1. Introduction

Pediatric-onset multiple sclerosis (POMS) is diagnosed in 3–5% of individuals with MS (Otallah and Banwell, 2018). It is associated with a higher relapse rate (Otallah and Banwell, 2018), but as a same time has a slower progression rate than adult-onset MS (Renoux et al., 2008). Importantly, patients with POMS reach irreversible and permanent disability earlier in adult life than those with adult-onset MS (Renoux et al., 2008). POMS has also numerous symptomatic presentations, such as fatigue (Goretti et al., 2012; MacAllister et al., 2009), depression (Banwell and Anderson, 2005; MacAllister et al., 2007; Amato et al., 2008) and cognitive impairment (Banwell and Anderson, 2005; Amato et al., 2008; MacAllister et al., 2005) that occur at a relevant proportion at an early stage of the disease (Amato et al., 2008; Amato et al., 2016). These manifestations have considerable impact on academic achievement, social interactions and development, and quality of life (Banwell and Anderson, 2005; Amato et al., 2008; MacAllister et al., 2005). Measurement of health-related quality of life (HRQoL) in patients with chronic diseases has become an important tool (Varni et al., 2007) that may help to understand how the clinical course, level of disability, impairment of daily activity impacts quality of life of affected children. It has been suggested to be a more comprehensive measure than disability scales in assessing the burden of disease (Nortvedt et al., 1999). Loss of quality of life in POMS compared to the general population has been shown in several studies (MacAllister et al., 2009; Mowry et al., 2010; Holland et al., 2014; Self et al., 2018) associated with variables, such as an increased Expanded Disability Status Scale (EDSS) score (MacAllister et al., 2009; Mowry et al., 2010), non- white race (Mowry et al., 2010), depression and fatigue (MacAllister et al., 2009; Self et al., 2018). Differences in results might be due to different sample characteristics, loss of statistical power because of small sample sizes, due to missing matched controls or due to inappropriate measurement tools for children (MacAllister et al., 2009; Amato et al., 2008; Holland et al., 2014; Weisbrot et al., 2014). There is no study to date that has together investigated fatigue, depression and their effects on quality of life in a representative cohort of patients with POMs and well-matched HCs. Therefore, the aim of this study was to examine the relationship between depression, fatigue and HRQoL in a large cohort of patients with POMS and age- and education matched HCs by using age-appropriate assessment tools.

2. Material and methods

2.1. Subjects

In this cross-sectional study, patients with POMS were enrolled by 20 German and 2 Austrian Neuropaediatric Departments of University Hospitals and HCs by 6 German centers. Inclusion criteria for patients with POMS were according to the McDonald criteria 2010 (Polman et al., 2011) and age between 12 and 18 years. Patients admitted as inpatients due to an acute relapse were included in the study after completion of intravenous steroid treatment. HCs were included if they were between 12 and 18 years old. Patients were excluded if they had any other demyelinating disease than MS such as acute disseminated encephalomyelitis (ADEM). Patients and HCs were excluded for the following reasons: no command of the German language; temperature > 37.5 °C; intravenous steroid treatment; history of any other neurological or psychiatric disease; neurological or psychiatric symptoms; illness that would preclude them from testing.

Recruitment for HCs was stratified for age (12–18 years) and education (secondary school and grammar school). In each age level, 15 HCs were recruited who attended secondary school and 15 HCs who attended grammar school ($n = 210$, 7 groups).

Ethical approval was received from the ethical committees of all participating study-sites and written consent was obtained from all subjects and parents.

2.2. Clinical, neuropsychological, depression, HRQoL and fatigue assessment

Demographic data (age, sex, years of education, type of school) of all subjects and clinical information of the patients, such as age of onset, disease duration, number of relapses, neurological symptoms at onset and at test date, medication and the EDSS score of all MS patients were recorded.

In 12-year old subjects, depression was evaluated with the Depressionstest für Kinder [DTK] (Rossmann, 2005), a German self-report questionnaire consisting of 55 items, evaluating three affective dimensions [dysphoric feeling and problems with self-worth (scale 1), agitated behavior (scale 2) and psychosomatic aspects of depression (scale 3)]. Depression was defined by a sum score of scale 1 and scale 2 ≥ 17 (Rossmann, 2005).

Subjects, who were 13 years old or older, were tested for depression by the German version of the Beck Depression Inventory [BDI-II] (Hautzinger et al., 2006). It is a 21-item self-report questionnaire covering cognitive, affective, physical and behavioral dimensions on a 4-point scale (0–3) and based on symptoms that were experienced during the last two weeks. The cut-off for depression was defined as a sum score of ≥ 14 [mild depression corresponding to 14–19, moderate depression to 20–28 and severe depression to 29–63 points] (Hautzinger et al., 2006). Given the small number of MS patients assessed with the DTK, further statistical analyses were performed exclusively with BDI-II sum scores (patients $n = 92$, HCs $n = 145$).

Quality of life was measured with the German version of the Pediatric Quality of Life Inventory™ version 4.0 (PedsQL™ 4.0) Generic Core Scale child self-report and parent proxy-reports for the age-ranges "8–12 years" and "13–18 years" (Varni et al., 2001; Felder-Puig et al., 2004). Questionnaires were evaluated according to the PedsQL™ scoring guidelines and have been reported previously (Varni et al., 2001). The questions are concerned how much of a problem has been experienced during the past four weeks on a 5-point-likert-scale. The scores were linearly transformed to a 0–100 scale, higher scores indicating a better HRQoL.

Fatigue was evaluated with the German version of the PedsQL™ Multidimensional Fatique Scale using the child (MacAllister et al., 2005; Amato et al., 2016; Varni et al., 2007; Nortvedt et al., 1999; Mowry et al., 2010) and the adolescents (Holland et al., 2014; Self et al., 2018; Weisbrot et al., 2014; Polman et al., 2011; Rossmann, 2005; Hautzinger et al., 2006) self-report form and parent-proxy-report form (Varni et al., 2004). The format, instructions and scoring algorithm are identical to the PedsQL™ 4.0 Generic Core Scale, with higher scores indicating lower fatigue symptoms.

Patient's HRQoL and fatigue were considered mildly impaired if the scale score fell between one and two standard deviations, and severely impaired if the scale score fell more than two standard deviations below the score of HCs (MacAllister et al., 2009).

Testing of depression, fatigue and HRQoL was conducted in the same order for all subjects at one day by trained staff.

2.3. Statistical analysis

Comparisons of subject's characteristics were analyzed by Student's t-test or the Mann-Whitney-U test depending on data distribution. Comparisons of relative frequencies were done with Chi-square analysis. Paired t-tests were used to determine the difference between parents and their children. The concordance between patient self-report and parent proxy-report was determined through Intraclass Correlation Coefficients (ICCs) and effect sizes were calculated as published previously (Varni et al., 2007).

Linear regression modeling was used to assess the independent contribution of variables. All variables were tested for collinearity. Demographic variables included age, type of school (secondary school vs. grammar school), years of education and sex. Disease related

Table 1
Characteristics of the study population

Characteristics	MS patients (n = 106)	HCs (n = 210)	*p*
Mean age ± *SD*	15.71 (1.63)	15.00 (2.0)	0.003*
range	(12-18)	(12-18)	
Female, n (%)	76 (71.7)	95 (45.2)	0.000***
Type of school			
Secondary school, n (%)	55 (51.9%)	97 (46.2)	0.343.***
Grammar school, n (%)	51 (46.2%)	113 (53.8%)	
Mean years of education (*SD*)	9.26 (1.52)	8.84 (1.95)	0.05**
Mean age at onset (*SD*)	14.1 (2.4)		
range, years	(4-18)		
Mean MS-duration (*SD*)	18.6 (23.7)		
range, months	(0-152)		
Disease course	Relapsing-remitting		
Mean number of relapses since onset *(SD)*	1.9 (2.0)		
range	(0-10)		
Mean monthly relapse rate (*SD*)	0.17 (0.25)		
range	(0.00-1.2)		
Mean EDSS score (*SD*)	0.65 (1.09)		
range	(0-7.5)		
Disease modifying drug, n (%)	77 (72.6%)		

Legend: *SD*: standard deviation;
* Mann-Whitney-U-Test
** t-Test
*** χ^2

variables included disease duration, number of relapses since onset, current relapse, number of symptoms at onset, number of current symptoms, age at onset, EDSS score and treatment with disease modifying therapy. The alpha level was corrected using the Bonferroni method to $\alpha = 0.0125$. A multinomial logistic regression analysis was adopted to assess the risk for the diagnosis of a mild or severe depression, mild or severe fatigue and mild ore severe loss of HRQoL. Data analysis was conducted using the IBM SPSS, version 22.0 (IBM Corp., Armonk, NY, USA, 2013).

3. Results

Between June 2012 und January 2015 a total of 106 patients with POMS and 210 HCs were enrolled. Characteristics of the cohort are summarized in Table 1. A total of 15 patients (14.2%) reported an acute relapse at inclusion. Only one patient received symptomatic treatment for depression (sertraline), none received treatment for fatigue.

According to the DTK and BDI-II measures, significant more MS patients (21.7%) compared to HCs (11.4%) were diagnosed to be depressed ($p = 0.014$). Depression did not occur significantly more often in patients with an acute relapse compared to patients without an acute relapse (acute relapse 20% vs. no relapse 22.5%; $\chi^2 = 0.046$, $p = 1.0$).

In the subgroup analyzed by the BDI-II, 9.8% of MS patients displayed mild, 7.6% moderate and 6.5% severe depression, whereas 6.2% of HCs displayed mild, 2.1% moderate and 2.1% severe depression ($\chi^2 = 9.208$, $p = 0.027$). 72.4% of all treated patients received interferons. 41.8% of patients treated with interferons were diagnosed as depressed. There was no significant difference regarding the rates of depression between patients treated with interferons and without interferons ($\chi^2 = 0.280$, $p = 0.689$).

In a multinomial logistic regression analysis, the diagnosis of MS significantly predicted the likelihood of being diagnosed with a moderate depression (Wald = 4.316, $p = 0.038$). No significant group difference was found for the likelihood of being either mildly or severely depressed. MS patients are 4.3 times more likely to be diagnosed with a moderate depression compared to HCs.

The linear regression analysis revealed that the model including age, sex, IQ, years of education, disease duration, EDSS score, number of symptoms at onset and disease-modifying therapy explained only 4% of variance within the BDI-II sum score ($R^2 = 0.044$, F (7,82) = 1.583, $p = 0.152$). Fatigue was identified to be independently associated with depression in MS patients ($R^2 = 0.518$, F (1,90) = 96.75, $p < 0.001$) and accounted for 51.8% of the variance of the BDI-II sum score. For every additional point on the BDI-II scale, patients had 0.655 points less on the (negatively coded) fatigue scale. 91.3% of all depressed patients were also fatigued, whereas only 50% of all depressed HCs were fatigued.

Interestingly, patients with an acute relapse did not differ significantly in respect to all three dimensions of fatigue and the Total Fatigue Scale from patients without an acute relapse. Nonetheless, patients were significantly more fatigued in respect to all three fatigue dimensions and the Total Fatigue Scale compared to HCs by self- and proxy-report (Table 2). Agreement between the juveniles and their parents was found to be moderate to good. Intraclass correlation coefficients ranged from 0.55 for the Cognitive Fatigue Scale, 0.58 for the Sleep/Rest Fatique Scale and for the General Fatigue Scale and 0.63 for the Total Fatigue Scale.

While parents of MS patients reported significantly lower fatigue scores for their children in the General Fatigue Scale ($p = 0.045$), all other scales were reported similarly between children and parents. In contrast, HC parents reported significantly less fatigue for their children for all scales ($p < 0.001$, respectively) except for the General Fatigue Scale (Table 2).

The proportion of mild fatigue in all four scales of the self-report form was between 19.8% and 27.4% for patients compared to 11.5% and 18.2% for HCs. The proportion of severe fatigue among all scales was between 8.5% and 26.4% for patients, compared to 1.0% and 5.3%

Table 2
Results of the PedsQL™ Multidimensional Fatigue Scale self-report form and proxy-report form

Scale	MS patients		HCs		Comparison		
	no.	mean (*SD*)	no.	mean (*SD*)	Difference MS patients vs. HCs	*p**	Effect size**
Self-report							
General Fatigue	106	63.15 (25.73)	209	77.64 (17.83)	14.51	0.000	0.81
Sleep/rest Fatigue	106	55.46 (21.69)	209	63.15 (19.16)	7.68	0.003	0.40
Cognitive Fatigue	106	65.99 (26.36)	209	74.52 (20.76)	8.53	0.009	0.41
Total Fatigue	106	61.57 (20.78)	209	71.78 (15.58)	10.21	0.000	0.65
Proxy-report							
General Fatigue	98	59.40 (23.66)	206	78.55 (18.55)	19.15	0.000	1.03
Sleep/rest Fatigue	98	52.52 (23.2)	205	70.75 (21.52)	18.23	0.000	0.85
Cognitive Fatigue	98	71.55 (26.74)	205	81.77 (20.69)	10.22	0.005	0.49
Total Fatigue	98	61.5 (21.26)	206	77.01 (17.14)	15.51	0.000	0.90

Legend: no.: number of subjects, *SD*: standard deviation, HCs: healthy controls
* Mann-Whitney U-Test
** Effect sizes are designated as small (0.20), medium (0.50), and large (0.80)

Table 3
Classification of fatigue

	Total Fatigue		General Fatigue		Sleep/Rest Fatigue		Cognitive Fatigue	
	Pat.	HCs	Pat.	HCs	Pat.	HCs	Pat.	HCs
Self-report								
No fatigue (%)	59.4	82.8	53.8	83.3	70.8	83.7	60.4	79.9
Mild fatigue (%)	20.8	14.4	19.8	11.5	20.8	15.3	27.4	18.2
Severe (%)	19.8	2.9	26.4	5.3	8.5	1.0	12.3	1.9
χ^2	30.407		37.164		14.139		20.402	
p*	0.000		0.000		0.001		0.000	
Proxy-report								
No fatigue (%)	55.1	82.5	49	81.6	53.1	79.5	65.3	83.4
Mild fatigue (%)	24.5	11.7	30.6	13.1	31.6	18	18.4	10.7
Severe fatigue (%)	20.4	5.8	20.4	5.3	15.3	2.4	16.3	5.9
χ^2	27.127		35.557		28.620		13.601	
p*	0.000		0.000		0.000		0.000	

Legend: Subject's fatigue was considered as mildly impaired if the scale score fell between one and two standard deviations below and as severely impaired if the scale score fell three and more standard deviations below the scale of healthy controls (HCs).

* χ^2-test (comparison between patients and HCs)

for the HCs (Table 3).

MS patients were identified to be at a twofold risk to have mild (Wald = 4.879, $p = 0.027$) and to be at a 9.6-fold risk to have severe fatigue (Wald 21.704, $p < 0.001$) compared to HCs.

Female gender was independently associated with fatigue ($B = -13.523$, $p < 0.001$). This model with clinical characteristics predicted 11.9% of variance of self-reported fatigue scores ($R^2 = 0.119$, $F(7,96) = 2.986$, $p < 0.007$). Total Fatigue Scale Scores did not differ significantly between patients treated with interferon-beta and patients not receiving any treatment (61,7 ± 20.2; $n = 56$ vs. 62,85 ± 19,83; $n = 29$; $p = 0.8$).

Furthermore, depression significantly predicted 51.8% of the variance of the Total Fatigue Score ($p < 0.001$).

Self-reported HRQoL was significantly lower across all domains in MS patients compared to HCs except for the Social Functioning Scale (Table 4). These differences were also reported in the proxy-report forms (Table 4). MS-Patients with an acute relapse did not have significant lower HRQoL compared to MS patients without an acute relapse regarding all dimensions (physical: $p = 0.044$, emotional: $p = 0.183$, social: $p = 0.129$, school: $p = 0.327$) and the Total HRQoL Scale Score ($p = 0.033$) after Bonferoni correction. MS patients demonstrated significant lower scores in cognitive as well as disability-related aspects of everyday school functioning (forgetting things at school (49.51 ± 31.1 vs. 60.32 ± 30.8; $p = 0.004$), missing school because of not feeling well (63.83 ± 36.34 vs. 84.18 ± 24.52; $p < 0,001$), missing school because of going to the doctor or hospital (55.83 ± 35.21 vs. 86.84 ± 24.36; $p < 0.001$) in comparison to HCs.

Cognitive fatigue was significantly correlated with all dimensions of HRQoL, although the highest correlation coefficient was observed for the school functioning dimension ($r = 0.770$, $p < 0.001$) and the Total HRQoL Scale Score ($r = 0.658$, $p < 0.001$).

Agreement between juveniles and parents was generally good with an ICC of 0.77 for the Physical Health Scale, 0.63 for the Emotional Functioning Scale, 0.61 for the Social Functioning Scale, 0.74 for the School Functioning Scale and 0.73 for the Total Score Scale. While parents of MS patients perceived HRQoL in their children identically as their children, parents of HCs scored significantly higher for their children for the Physical Health Scale ($p < 0.001$), School Functioning Scale ($p = 0.002$) and the Total HRQoL Scale ($p < 0.001$).

In the self-report form, the proportion of mildly affected HRQoL for all scales ranged between 10.4% and 25.5% for MS patients compared to 4.8% and 15.0% for HCs. The proportion of severely impaired HRQoL in these domains ranged between 10.4% and 27.4% for MS patients compared to 2.9% and 7.2% for HCs (Table 5). There was a significant difference between patients and HCs regarding the severity-classification of all scales except for the social subscale.

Based on the multinomial logistic regression analysis of the self-report form, the risk for a mildly reduced HRQoL was three-times higher (Wald = 13.379, $p < 0.001$) and for severely reduced HRQoL 9-times higher (Wald = 20.557, $p < 0.001$) in MS patients compared

Table 4
Results of the PedsQL™ Generic Core Scale self-report form and proxy-report form

Scale	MS patien		HCs		Comparison		
	no.	mean (*SD*)	no.	mean (*SD*)	Difference MS patients vs. HCs	p*	Effect size**
Self-report							
Physical health	106	74.62 (22.1)	207	86.67 (13.64)	12.05	0.000	0.88
Emotional functioning	106	63.35 (24.89)	207	71.89 (21.21)	8.55	0.000	0.40
Social functioning	106	88.73 (17.01)	207	91.96 (12.66)	3.23	0.581	0.25
School functioning	103	58.15 (24.74)	207	71.88 (19.14)	13.73	0.000	0.72
Total HRQoL Scale	106	71.81 (18.36)	207	81.39 (13.38)	9.58	0.000	0.71
Proxy-report							
Physical health	99	76.57 (20.98)	206	90.55 (11.96)	13.98	0.000	1.17
Emotional functioning	98	62.3 (25.18)	206	75.06 (20.67)	12.76	0.004	0.62
Social functioning	98	87.4 (18.74)	206	93.63 (12.44)	6.23	0.015	0.26
School functioning	94	60.56 (25.10)	206	76.29 (20.19)	15.73	0.000	0.77
Total HRQoL Scale	98	72.28 (18.04)	206	84.75 (12.73)	12.47	0.000	0.90

Legend: no.: number of subjects; *SD*: standard deviation; HCs: healthy controls

* Mann-Whitney U-Test

** Effect sizes are designated as small (0.20), medium (0.50), and large (0.80)

Table 5
Classification of HRQoL

	Total		Physical		Emotional		Social		School	
	Pat.	HCs	Pat.	HCs	Pat.	HCs	Pat.	HCs	Pat.	HCs
Self-report										
No (%)	56.6	85.0	57.5	84.1	72.6	86	79.2	87.9	59.2	82.1
Mild (%)	25.5	12.1	15.1	11.6	16.0	10.1	10.4	4.8	23.3	15.0
Severe (%)	17.9	2.9	27.4	4.3	11.3	3.9	10.4	7.2	17.5	2.9
χ^2	34.896		37.808		9.637		4.663		26.405	
p	0.000		0.000		0.008		0.097		0.000	
Proxy-report										
No (%)	74.5	94.7	56.1	82.5	66.3	85.4	77.6	92.7	51.1	79.6
Mild (%)	18.4	4.4	15.3	11.2	17.3	10.7	9.2	4.4	36.2	16.5
Severe (%)	7.1	1.0	28.6	6.3	16.3	3.9	13.3	2.9	12.8	3.9
χ^2	26.261		31.575		18.384		15.727		26.095	
p	0.000		0.000		0.000		0.000		0.000	

Legend: Patient's HRQoL was considered as mildly impaired if the scale score fell between one and two standard deviations and as severely impaired if the scale score fell three and more standard deviations below the scale of HCs
χ^2-test (comparison between patients and HCs)

to HCs.

Analyzing demographic and clinical factors, EDSS ($B = -4.645$, $p < 0.001$) was identified as a significant predictor for HRQoL ($R^2 = 0.145$, $F(7,96) = 3.496$, $p = 0.002$). A higher EDSS was significantly associated with lower HRQoL. The model predicted 14.5% of variance within the self-report form of the Total HRQoL Scale.

A further linear regression analysis was conducted to predict HRQoL based on the level of depression, as measured by the BDI-II sum score, and on the level of fatigue, measured by the Total Fatigue Scale score self-reported. The regression equation was significant ($R^2 = 0.677$, $F(2,89) = 93.429$, $p < 0.001$), predicting 67.7% of variance within Total HRQoL Scale score. Poorer HRQoL was significantly associated with the diagnosis of depression ($B = -1.01$, $p < 0.001$). The partial correlation between depression and HRQoL (pr $= -0.516$) revealed that depression uniquely predicted 26.6% of the variance for the self-reported Total HRQoL Scale score. Subjects with depression demonstrated significant lower scores in the Total HRQoL Scale (patients: $M = 51.84$, $SD = 14.71$; HCs: $M = 64.44$, $SD = 14.77$; $p = 0.008$) compared to subjects without depression (patients: $M = 77.52$, SD $= 14.71$; HCs: $M = 83.48$, $SD = 11.59$; $p = 0.002$).

Fatigue also significantly predicted self-reported HRQoL ($B = 0.343$, $p < 0.001$). Poorer HRQoL was associated with increasing level of fatigue. Level of fatigue uniquely predicted 18.7% of the variance for Total HRQoL Scale score analyzed by a partial correlation (pr $= 0.433$).

4. Discussion

We investigated rates of depression and fatigue and their effects on HRQoL in a representative cohort of patients with POMS compared to age-matched HCs.

In line with a previously reported study (Goretti et al., 2012), the rate of depression was twice as high in patients compared to HCs, though in other investigations the prevalence of depressive symptoms differed possibly due to differences in assessment tools and sample characteristics (Amato et al., 2008; Weisbrot et al., 2014; Parrish et al., 2013; Amato et al., 2014). Furthermore, we demonstrate that patients are significantly more often diagnosed with mild, moderate and severe depression compared to HCs and that they are at an increased risk of moderate depression. Depression was not related to interferon treatment. Depression was also not associated with EDSS or other clinical characteristics, but we confirmed a strong association between depression and fatigue. This relationship is complex since experience of fatigue could be caused by depressive feelings and severe fatigue might induce depression (Ketelslegers et al., 2010). Other factors, such as lesion load and localization (Feinstein et al., 2004), disability, uncertainty, hope and coping (Lynch et al., 2001), that have been reported to account to up to 40% of the variance of depression, have not been investigated in this study.

Patients with POMS were 2.3-times more often fatigued than HCs indicating that fatigue is a common problem in patients with POMS (Goretti et al., 2012; MacAllister et al., 2009; Amato et al., 2008; Holland et al., 2014; Amato et al., 2014; Amato et al., 2010). We found all three dimensions of fatigue to be affected, which is in accordance to a previous study (MacAllister et al., 2009). In our population, the calculated risk was 2-fold increased for mild fatigue and 9.6-fold increased for severe fatigue in comparison to HCs. Fatigue was significantly associated with female gender and depression, while it was unrelated to other clinical factors and whether they received medication, such as interferon-beta, or not. This is also consistent with studies in adult MS (Carroll et al., 2016). The association of female gender and fatigue has been detailed in children with physical disabilities (Maher et al., 2015) and in healthy adolescents (ter Wolbeek et al., 2006) and might be explained by a differential developmental course in bodily processes or by the role of hormonal factors in the development of mental disorders of females around this age (Nolen-Hoeksema and Girgus, 1994).

In accordance with other studies (MacAllister et al., 2009; Mowry et al., 2010; Self et al., 2018) our patients experienced significant lower self-reported and proxy-reported HRQoL. Physical and school-related dimensions of HRQoL were predominantly affected both self- and proxy-reported, which is in accordance to the findings of other pediatric studies (MacAllister et al., 2009; Self et al., 2018). Every kind of physical impairment, although disability is mild in patients with POMS, or every change in school functioning, such as high absenteeism or learning problems, may contribute to lower HRQoL.

In contrast, the emotional dimension of HRQoL seemed to be less impaired in these patients. This finding differs from other reports and may be explained by cultural differences in reporting or different sample characteristics (Mowry et al., 2010; Self et al., 2018). Interestingly, the social functioning dimension was the least affected in our study, which is congruent to other studies (MacAllister et al., 2009; Self et al., 2018). This indicates that MS patients are well socially integrated despite their disease or physical impairment and are well socially accepted in their peer groups at an early stage of their disease. Furthermore, we confirmed the finding that EDSS positively correlated with the level of HRQoL and in particular with the physical and social dimension (MacAllister et al., 2009; Mowry et al., 2010; Self et al., 2018). This suggests that as physical disability increases, social interactions are limited as patients are not able to keep up with their peers or as they can't do things that others their age can do. Not surprisingly, fatigue and depression were both independent contributors to HRQoL in our study as this has already been described in adults (Amato et al., 2001). Associations between depression and HRQoL (Krysko and O'Connor, 2016) and fatigue and HRQoL (MacAllister et al., 2009; Self et al., 2018) have been investigated without mentioning its explanatory value for these measures. We were able to demonstrate that fatigue by itself accounted one fifth and depression by itself almost one fourth of the variance of HRQoL and that the presence of depression and fatigue explained a total of 67.7% of variance of HRQoL. These findings may therefore have important implications for patient management. As a consequence, even in patients with a short disease duration fatigue and depression should be screened for as mild symptoms may be overlooked easily. Furthermore, treatment of depression and fatigue could improve HRQoL effectively and would have an important impact on school functioning.

Cross-informant variance was only documented for the General Fatigue Scale in MS patients. All other ratings of fatigue and HRQoL in MS-patients and their parents were quite congruent. This is in accordance to systematic reviews that endorse a good agreement between parents and their chronically ill children in domains reflecting physical activity, social functioning or disease related symptoms compared to healthy children (Eiser and Morse, 2001). This again emphasizes the important role of family relationships for successful coping and adjustment-strategies in individuals with MS. However, there might be a higher tendency to overestimate fatigue or to misinterpret depressive symptoms in their sick children. Participating in MS-educational programs might help to improve the parent-child relationship and the perception of the disease.

The interpretation of this study is limited to the cross-sectional study design and does not allow for causal inferences to be made, hence longitudinal studies examining the treatment effects on depression, fatigue and effects on HRQoL are needed.

In summary, patients with POMS experienced not only significantly greater fatigue and were also more often depressed than HCs, they also experienced a greater loss of HRQoL. Our present study demonstrates that patients with POMS are at an increased risk for moderate depression, mild to severe fatigue and mild to severe loss of HRQoL. Our data support the assumption that these comorbidities and loss of HRQoL already occur at a very early stage in juvenile MS.

We identified depression and fatigue as the most important predictors with a large impact on HRQoL. Children and adolescents with MS should therefore be vigilantly screened for depression and fatigue regardless of a short disease and of the severity of clinical disability. Incorporating these comorbidities in future therapeutic trials seem mandatory to capture the global impact of MS in young patients.

Declaration of Competing Interest

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