MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 5761-5770
DOI: 10.12659/MSM.909183

Received: 2018.01.26
Accepted: 2018.04.18
Published: 2018.08.18

Effect of Rehabilitation on Fatigue Level in Patients with Multiple Sclerosis

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Source of support: Departmental sources

Background: The objective of this study was to evaluate the effect of a rehabilitation program in changing the perception of fatigue in patients with multiple sclerosis.

Material/Methods: The study involved 65 respondents/patients with clinically confirmed multiple sclerosis (54 women, 11 men, average age 46.49 years). The evaluation of the effects of fatigue on the physical, psychological, and psychosocial aspects of life was assessed using the Modified Fatigue Impact Scale (MFIS). To test the effectiveness of the neurorehabilitation program, we enrolled 2 groups: the experimental group (EG, n=32, 29 women, 3 men, Expanded Disability Status Scale (EDSS) 4.8 average, SD±1.77, min. 1.5 max 8.0) participated in the intervention and rehabilitation program over a period of 12 weeks and the control group (CG, n=33, 25 women, 8 men. EDSS average 5.12±1.74 SD, min. 2.0 max. 8.0). Each group of patients was divided into 3 sub-groups according to the severity of EDSS: a) 1–3.5, b) 4–6, and c) 6.5–8. For the statistical evaluation of the significance of the observed changes, the MANOVA/ANOVA model was used.

Results: Between the input and output assessment of the MFIS individual areas questionnaire between the EG and the CG, there existed a statistically significant in the physical area ($p<0.000$), psychological area ($p<0.000$), and psychosocial area ($p=0.002$).

Conclusions: Our results support the importance of an active approach in patients with multiple sclerosis using individualized rehabilitation intervention programs.

MeSH Keywords: Fatigue • Multiple Sclerosis • Rehabilitation

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/909183

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Background

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, causing the demyelization of nerve fibres and their direct loss. At present, it is included among autoimmune diseases in which the immune response is directed against myelin antigens [1]. The therapeutic approach to a patient with an MS diagnosis should include optimal medical therapy and regular physiotherapy at all stages of the disease. It is a progressive disease with a wide spectrum of neurological images. The rehabilitation program must therefore be individualized, with an emphasis on the clinical picture and course of the disability evolving over time [2–6]. Fatigue is one of the symptoms most frequently reported by MS patients [7]. According to various studies, fatigue is reported by 75–95% of patients during the disease course [3,4,8,9]. Fatigue also imposes significant socioeconomic consequences [10,11] and fatigue is considered to be one of the main causes of impaired quality of life among MS patients [8,11,13]. Especially for patients with minor disabilities, it is a major problem causing unemployment [8,13]. Fatigue was defined by the Multiple Sclerosis Council for Clinical Practice Guidelines in 1998 [7] as a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities [4,7,13]. In many studies, the positive impact of regular physiotherapy on the perception of fatigue, the physical and mental condition of patients, the level of disability, and quality of life were reported [2,3,6,14,15], but few studies have exclusively examined the effectiveness of physiotherapy for people more severely affected by MS (EDSS 6.5–8). The aim of this paper is to assess the effect of physiotherapy in the management of fatigue in patients with multiple sclerosis, regardless of the disability level.

Material and Methods

The research was conducted in cooperation with the Slovak Association of Multiple Sclerosis and Center for the Treatment and Diagnosis of Multiple Sclerosis of J.A. Reiman Hospital in Prešov, Slovakia. Patients were included in the research after providing informed consent. Subjects had a clinical and laboratory confirmed diagnosis of multiple sclerosis and an Extended Disability Status Scale (EDSS) of 1.5 to 8. The study included 84 patients with confirmed diagnosis of MS according to the Mc Donald criteria (2001, 2010) [16,17], and we used Poser´s criteria (1983) [18] for patients with longer duration of disease. The inclusion criterion was MS patient with adequate cognitive function, as assessed by a Mini-Mental State Examination score of 23 or over. The exclusion criteria were regular outpatient rehabilitation treatment, a disability level greater than 8 according to the EDSS, acute attacks of the disease 3 months before the assessment, and cognitive deficits. Additional exclusion criteria were major depression assessed respectively by the Beck Depression Inventory (>17 points), age less than 18 years, and unwillingness to cooperate. Of the 84 interviewed patients, 65 patients met the criteria.

The study included 65 patients with multiple sclerosis. The association of the impact of selected factors on the change of monitored parameters was performed in all patients in the monitored group. To test the effectiveness of the neuro-rehabilitation program, we divided the patients into 2 groups. The experimental group (EG=32) consisted of patients who participated in the intervention rehabilitation program for 12 weeks. The control group (CG=33) comprised patients who, did not undergo the rehabilitation treatment, as they were included in a waiting list for it.

We divided the patients into groups according to the Kurtzke Extended Disability Status Scale, which in clinical practice is the most widely used scale to assess the disability level in MS patients [19]. Patients were divided into 3 groups according to the disability level. The first group included patients with EDSS 1–3.5, the second with EDSS 4–6, and the third with EDSS 6.5–8.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Interventions

Rehabilitation interventions consisted of exercise 3 times per week for 12 weeks (36 sessions). The rehabilitation program was determined individually for each patient, focusing on clinical status and course of the disease. In patients with a lower disability level, we focused on conditioning and used methods aimed at total relaxation. In patients with moderate disability, we focused on alleviating symptoms, with special attention to patients with a high disease level for individual treatment. Physiotherapy techniques and procedures based on a neurophysiological basis were applied during the treatment. Exercises varied between gradual stretching, resistance, and aerobic training, cycling, stair-climbing training, and walking. All patients underwent an educational program focused on treatment options for disease symptoms.

Measurements

Patients were examined at the beginning and end of the rehabilitation intervention. The examination included socio-demographic and clinical data of the respondents, level of disability, fatigue, depression, and cognitive impairment. We collected data on age, gender, education, working ability, length of

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disease, type of MS, relapse, immunomodulation treatment and length of use, and previous experience with physical activity and rehabilitation treatment.

The EDSS was used to determine level of disability. The EDSS is a physician-determined measure of impairment for assessing MS subjects. The EDSS is an index of MS severity ranging from 0 (normal) to 10 (death). To maximize reproducibility, a single neurologist whose level of intra-rater reliability was high (intra-class correlation coefficient, 0.92) performed these assessments [19–21].

The Modified Fatigue Impact Scale (MFIS) was used for assessing the impact of comprehensive rehabilitation to reduce the sense of fatigue in patients. In 1998, for use in clinical practice and research, the shortened 21-point version of the FIS-Modified Fatigue Impact Scale (MFIS) was recommended. The MFIS is a component of the "MS Quality of Life Inventory" range. The MFIS assesses the impact of fatigue on the physical, mental, and psychosocial life of patients. Respondents rated each item from 0 points (no problem) to 4 points (extreme problem). Patient were asked to assess their feelings in the last month. The total score range was from 0 to 84 points. The under-range assessment of the physical condition is rated from 0 (less fatigue) to 36 (maximum fatigue), the cognitive under-range in the range from 0 to 40 points, and the psychosocial under-range from 0 to 8 points. More points meant a greater impact of fatigue on the physical, cognitive, and psychosocial areas and has a coefficient alpha of 0.81 [21–23].

The Beck Depression Inventory (BDI) was to measure depression, with a cut-off off <17 points for entry into the study. A score of 18 or higher on the depression scale was classified as depression [21,24].

The Mini-Mental State Examination (MMSE) or Folstein test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment [25].

Statistical analysis

Demographic variables and baseline clinical variables were assessed using descriptive statistics. The evaluation was performed by comparing 2 groups of patients – the experimental group and the control group – before initiation of the treatment (baseline measurements) and after the 12-week individual rehabilitation program. For the statistical evaluation of the significance of the observed treatment effects, we used the MANOVA/ANOVA model. The assessment of the influence of selected predictors on the change of the individual dimensions of the fatigue scale after completing the rehabilitation program was performed by linear regression. The statistical analysis was performed using IBM SPSS 19 software.

Results

The socio-demographic and clinical data of the respondents according to the monitored groups are presented in Table 1. Sixty-five patients with clinically confirmed MS participated in the research; they had an average age of 46.49 years (SD±10.43 min. 21, max. 66) and consisted of 11 men (16.9%) and 54 women (83.1%). In the experimental group, there were 29 women (90.6%) and 3 men (9.4%). In the control group there were 25 women (75.8%) and 8 men (24.2%). Regarding education level, 84.6% of respondents had completed high school, 3.1% completed elementary school, and 12.3% had a university degree. In both group combined, 53 (81.5%) of respondents had a disability pension, 7 (10.8%) were working full-time, and 5 (7.7%) did part-time work. Five (15.6%) respondents in the experimental group and 2 (6.1%) respondents in the control group stated they could work without restriction. Fifty (75.4%) had been diagnosed with MS for more than 9 years. In both groups, most patients had a disease duration of 9 years and more. In the whole study population, 47 respondents (72.3%) rated the course of their disease as relapsing-remitting, 3 respondents (4.6%) as primarily progressive, 13 respondents (20.0%) as secondarily progressive, and 2 respondents (3.1%) as progressively relapsing. The average EDSS value in the experimental group was 4.8±1.77 points and 5.12±1.74 points in the control group. Immunomodulatory treatment was indicated for 25 (38.5%) respondents from the whole study population. In the experimental group, 13 respondents received immunomodulatory treatment, with an average length of 2.31±2.9 years. In the control group, 12 respondents received immunomodulatory treatment, with an average length of 1.79±2.68 years.

At the beginning of our research, the respondents assessed the physical, psychological, and psychosocial impact of fatigue using the standardized MFIS questionnaire. After completing the 12-week intervention rehabilitation program, patients from the experimental group had follow-up examinations. We conducted a comparative examination with the control group patients. The results of the MANOVA statistical analysis of the individual MFIS under-range values of the acquired EG and CG respondents during the input and output of the measurement are shown in Table 2. Table 3 shows the reported results of the MANOVA statistical analysis comparison of the MFIS values range in the EG and CG before and after rehabilitation treatment, according to disability level.

Statistical indicators for the impact of the intervention rehabilitation program in changing the average values of the individual MFIS categories of the study monitored depending on the disability level are presented in Tables 4 and 5.

For statistical evaluation, we used a multidimensional (multivariate) variance analysis (MANOVA). Since P (measurement * group)

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Table 1. Socio-demographic and clinical data of experimental and control group patients.

	Experimental group (EG)	Control group (CG)	Together
Number of patients (n)	32	33	65
Age (years ±SD)	44.22±10.80 min. 21 max.66	48.73±9.70 min. 25 max.65	46.49 ±10.43 min.21 max.66
Gender			
Men	3 (9.4%)	8 (24.2%)	11 (16.9%)
Women	29 (90.6%)	25 (75.8%)	54 (83.1%)
Education			
Elementary	2 (6.2%)	0 (0%)	2 (3.1%)
High school	25 (78.1%)	30 (90.9%)	55 (84.6%)
Higher education	5 (15.6%)	3 (9.1%)	8 (12.3%)
Work capacity			
Without restrictions	5 (15.6%)	2 (6.1%)	7 (10.8%)
With restrictions	2 (6.2%)	3 (9.1%)	5 (7.7%)
Disability pension	25 (78.1%)	28 (84.8%)	53 (81.5%)
Disease duration			
Up to 1 year	0 (0%)	1 (3%)	1 (1.5%)
1 –4 years	3 (9.4%)	5 (15.2%)	8 (13.8%)
5–8 years	3 (9.4%)	3 (9.1%)	6 (9.2%)
9 years and more	26 (81.2%)	24 (72.7%)	50 (75.4%)
Course of disease			
Relapsing remitting	23 (71.9%)	24 (72.7%)	47 (72.3%)
Primarily progressive	0 (0%)	3 (9.1%)	3 (4.6%)
Secondarily progressive	7 (21.9%)	6 (18.2%)	13 (20.0%)
Progressively relapsing	2 (6.2%)	0 (0%)	2 (3.1%)
EDSS (n ±SD)	4.8±1.77 min. 1.5 max. 8	5.12±1.74 min. 2 max. 8	4.98±1.74 min.1.5 max.8
EDSS 1–3.5	9 (28.1%)	7 (21.2%)	16 (24.6%)
EDSS 4–6	16 (50.0%)	17 (51.5%)	33 (50.7%)
EDSS 6.5–8	7 (21.9%)	9 (27.3%)	16 (24.6%)
Immunomodulatory therapy			
Yes	13 (40.6%)	12 (36.4%)	25 (38.5%)
No	19 (59.4%)	21 (63.6%)	40 (61.5%)
Length of immunomodulatory therapy (years ±SD)	2.31±2.9 min. 0 max. 8	1.79±2.68 min. 0 max. 8	1.86±2.76 min. 0 max. 8

≤0.05, the average is at least 1 of the 3 statistically different variables (measurement 1 *versus* measurement 2) between the 2 groups for 5% alpha. The differences between groups according to the disability level as measured by EDSS nor its interaction were not statistically significant (Table 4).

The average value of physical area fatigue in the EG was 24.06 points ±1.3 in the output measurements, and 21.44 points ±1.2 after completing the rehabilitation program. The average value of the monitored variables evaluated in the CG was 22.27 points ±1.3 in the input measurement and 23.03 points ±1.2 in the output measurement. In the experimental group, we observed a reduction of the impact on fatigue in the physical area. In contrast, there was a slight increase in the average values of the monitored variables in the control group. We demonstrated a significant change of the average values of the level of statistical significance $p<0.000$ in the EG compared with the CG.

The average MFIS value demonstrate that the impact of fatigue in the mental area in the input examination with the EG was 20.67 points ±1.5. After completing the intervention rehabilitation program, the values decreased to 17.67 points ±1.4. In the CG, the value of the input examination amounted to 21.22 points ±1.4 and 21.69 points ±1.4 with the output exam. We found a significant change in the average values

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Table 2. The comparison averaged scores fatigue scales for patients experimental and control group before and after rehabilitation treatment.

Variable	Group	Measurement	Mean	SD	95% confidence intervals	
					Lower bound	Upper bound
Physical functioning	E	1	24.068	1.314	21.439	26.698
		2	21.448	1.227	18.993	23.903
	C	1	22.273	1.306	19.659	24.887
		2	23.036	1.220	20.596	25.477
Cognitive functioning	E	1	20.679	1.458	17.762	23.596
		2	17.676	1.396	14.882	20.470
	C	1	21.225	1.449	18.325	24.125
		2	21.693	1.388	18.916	24.471
Psychosocial functioning	E	1	4.738	0.340	4.058	5.419
		2	4.231	0.340	3.552	4.911
	C	1	4.556	0.338	3.879	5.232
		2	4.743	0.338	4.067	5.419
MFIS	E	1	49.486	2.854	43.775	55.197
		2	43.355	2.740	37.873	48.838
	C	1	48.054	2.838	42.376	53.731
		2	49.473	2.724	44.023	54.924

MFIS – Modified Fatigue Impact Scale (no problem: 0, extreme problem 80); group: E – experimental, C – control; measurement: 1 – before training, 2 – after training;

Table 3. The comparison averaged scores fatigue scales for patients experimental and control group before and after rehabilitation treatment depending on the disability level.

Variable	Group	EDSS	Measurement	Mean	SD	95% confidence intervals	
						Upper bound	Lower bound
Physical functioning	E	1	1	20.000	2.336	15.327	24.673
			2	16.111	2.181	11.747	20.475
		2	1	22.062	1.752	18.557	25.568
			2	20.375	1.636	17.102	23.648
		3	1	30.143	2.648	24.844	35.442
			2	27.857	2.473	22.909	32.805
	C	1	1	16.714	2.648	11.415	22.013
			2	18.286	2.473	13.338	23.234
		2	1	22.882	1.699	19.482	26.283
			2	22.824	1.587	19.648	25.999
		3	1	27.222	2.336	22.549	31.896
			2	28.000	2.181	23.636	32.364

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Table 3 continued. The comparison averaged scores fatigue scales for patients experimental and control group before and after rehabilitation treatment depending on the disability level.

Variable	Group	EDSS	Measurement	Mean	SD	95% confidence intervals	
						Upper bound	Lower bound
Cognitive functioning	E	1	1	17.778	2.591	12.592	22.963
			2	14.778	2.482	9.811	19.745
		2	1	19.688	1.944	15.798	23.577
			2	17.250	1.862	13.525	20.975
		3	1	24.571	2.938	18.692	30.451
			2	21.000	2.815	15.368	26.632
	C	1	1	17.857	2.938	11.977	23.737
			2	17.714	2.815	12.082	23.346
		2	1	20.706	1.886	16.933	24.479
			2	21.588	1.806	17.974	25.202
		3	1	25.111	2.591	19.926	30.297
			2	25.778	2.482	20.811	30.745
Psychosocial functioning	E	1	1	3.778	0.604	2.568	4.987
			2	3.444	0.604	2.236	4.653
		2	1	4.437	0.453	3.530	5.345
			2	4.250	0.453	3.344	5.156
		3	1	6.000	0.685	4.628	7.372
			2	5.000	0.685	3.630	6.370
	C	1	1	3.857	0.685	2.486	5.229
			2	3.857	0.685	2.487	5.227
		2	1	4.588	0.440	3.708	5.468
			2	4.706	0.439	3.827	5.585
		3	1	5.222	0.604	4.013	6.432
			2	5.667	0.604	4.458	6.875
MFIS	E	1	1	41.556	5.074	31.403	51.708
			2	34.333	4.870	24.588	44.079
		2	1	46.188	3.805	38.573	53.802
			2	41.875	3.653	34.566	49.184
		3	1	60.714	5.753	49.203	72.226
			2	53.857	5.522	42.807	64.908
	C	1	1	38.429	5.753	26.917	49.940
			2	39.857	5.522	28.807	50.908
		2	1	48.176	3.692	40.790	55.563
			2	49.118	3.544	42.027	56.209
		3	1	57.556	5.074	47.403	67.708
			2	59.444	4.870	49.699	69.190

MFIS – Modified Fatigue Impact Scale; group: E – experimental, C – control; EDSS: 1 – (1–3.5), 2 – (4–6), 3 – (6.5–8); measurement: 1 – before training, 2 – after training.

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Table 4. Statistical indicator for the impact of the intervention rehabilitation program in changing the average values of the MFIS monitored depending on the disability level and power of study.

Effect		F	P	Partial Eta^2	Observed Power[a]
Intergroup	Intercept	224.542	0.000	0.910	1.000
	Group	1.187	0.323	0.006	0.091
	EDSS	3.657	0.002	0.190	0.911
	Group * EDSS	0.320	0.925	0.004	0.066
Intra-group	**Measurement**	5.350	**0.003**	0.206	0.971
	Measurement * group	13.926	**0.000**	0.400	1.000
	Measurement * EDSS	0.389	0.885	0.014	0.116
	Measurement * group * EDSS	1.846	0.096	0.038	0.244

Table 5. Statistical indicator for the impact of the intervention rehabilitation program in changing the average values of the individual MFIS categories.

Effect	Variable	F	P
Measurement	Physical functioning	5.576	**0.022**
	Cognitive functioning	10.705	**0.002**
	Psychosocial functioning	2.243	0.140
	MFIS	15.334	**0.000**
Measurement * group	Physical functioning	18.515	**0.000**
	Cognitive functioning	20.089	**0.000**
	Psychosocial functioning	10.587	**0.002**
	MFIS	39.384	**0.000**

p Values refer to the significance of change MFIS between the evaluation before and after rehab. program in the EG and CG using MANOVA test.

of the level of statistical significance p<0.000 in the EG compared with the CG.

In the psychosocial area, we did not find a significant change between measurements. The measurement of psychosocial area (both groups together) was not statistically significant (p=0.14) because the average of the 2 groups together did not change. What is important is the interaction of the measurement * group, showing that the average value in the EG decreased but in the CG the average value increased, and these differences were statistically significant (p=0.002).

The average value of the MFIS range in the EG decreased from 49.48 to 43.35 points, which shows the improved assessment of negative impacts of fatigue on the general health of the respondents in the EG. The average value of the MFIS range in the CG increased from 48.05 to 49.47. During the assessment of the average values in the MFIS questionnaire in the input and output EG and CG values, we found a significant change in the average values of the level of statistical significance p<0.000 in the experimental group in comparison with the control group.

After dividing patients into 3 sub-groups according to the disability level as measured by EDSS, with the first sub-group comprising patients with EDSS level 1–3.5, the second sub-group comprising patients with EDSS 4–6, and the third sub-group comprising patients with EDSS 6.5–8, we monitored the effectiveness of the rehabilitation interventions. The differences between the sub-groups and their interaction were not statistically significant. Our results show that with rehabilitation, we achieved similar results for all the respondents regardless of the disability level (Table 4).

We used linear regression to assess the influence of selected predictors on changing the dimensions of the fatigue scale after completing the rehabilitation program (Table 6). The predictors of change were selectively grouped by experimental or control group, age, duration of disease, and level of disability

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Table 6. Linear regression explaining change of the individual MFIS categories (standardized coefficients).

Parameter at baseline	MFIS P		MFIS C		MFIS PS		MFIS	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
R2	0.20	0.24	0.27	0.34	0.12	0.12	0.39	0.45
F	**15.818*** **	**4.693*** **	**23.511*** **	**7.844*** **	**8.303** **	2.037	**39.802*** **	**12.266*** **
R^2 change	0.20	0.04	0.27	0.07	0.12	0.003	0.39	0.06
F change	**15.818*** **	0.988	**23.511*** **	2.181	**8.303** **	0.071	**39.802*** **	2.279
β-group	**–0.45*** **	**–0.43*** **	**–0.52*** **	**–0.51*** **	**–0.34** **	**–0.33** **	**–0.62*** **	**–0.60*** **
β-age		0.16		0.22		0.05		0.22
β-leght of disease		0.11		0.14		0.02		0.13
β-EDSS		–0.06		–0.239		–0.02		–0.17

Predictors: a. group, b. group, EDSS, age, leght of disease.

according to the EDSS. Linear regression analysis results suggest that the only predictor influencing the change of MFIS sub-scales was the group assignment. Patients in the experimental group achieved statistically significant ($p<0.001$) changes in the MFIS physical, and cognitive fatigue, and the general score and psychosocial area fatigue were also statistically significant ($p<0.01$). Predictors such as age, disease length, and level of disability (EDSS) did not have a statistically significant effect on the observed parameters.

Discussion

Exercise therapy has the potential to induce a positive effect in MS fatigue, but findings are heterogeneous. Our results support regular physical activity as an approach for managing fatigue in patients with MS. Existing studies that assessed the impact of physical exercise to reduce fatigue include highly variable intervention programs and the effects achieved in the published studies are very different. One of the most commonly used therapies used to treat fatigue is aerobic training. Studies aimed at assessing the effect of applying aerobic exercise to reduce fatigue in MS patients show different results [2,15,26–28]. Rasova et al. [15] pointed to the positive impact of training on fatigue perceived by MFIS among patients enrolled with disability at EDSS ≤6.5. The exercise was performed on a bicycle with an intensity of 60% of VO max. and exercise time in the range of 2–30 min. The experimental group before and after the intervention, compared to the control group, demonstrated a statistically significant reduction in the impact of the fatigue of the individual life dimension [15]. Similarly, Huisinga et al. [29] demonstrated the positive impact of 12-week training to improve fatigue in MS patients with a degree of EDSS disability level 1–6. Fatigue was assessed using the Fatigue Severity Scale (FSS) and MFIS range. They observed an FSS improvement from 4.89±1.32 for 4.32 ($p=0.008$) and in MFIS from 43.7±15.8 for 35.4±14.3 ($p<0.001$). The reference data suggests that the physical fitness and feeling of fatigue in MS patients may be influenced by aerobic exercise. In a randomized study, Petajan et al. [30] demonstrated the positive impact of a 15-week aerobic training on the physical fitness of the subjects and improving the $VO_{2MAX.}$ value for level of statistical significance $p\leq0.05$. There was also improvement in fatigue in the experimental group after 10 weeks but not at the final assessment after 15 weeks. Rampello et al. [31] compared the effectiveness of aerobic training and neurophysiological training. The results demonstrate the improved effectiveness of aerobic training at maximum capacity and the gait in patients with mild and moderate disability. Aerobic training and neurological training demonstrated a similar impact on improving the assessment of the fatigue level and quality of life. Although many studies recommend aerobic training as fatigue therapy in patients with MS, there are many studies that question its effectiveness [32–34] and did not demonstrate improvement after aerobic training with the varying duration of the program. Mostert and Kesselring [32] assessed the effects of a short-term exercise training program on aerobic fitness, fatigue, health perception, and activity level of subjects with multiple sclerosis. MS patients were randomly assigned to an exercise training (MS-ET) or non-training group (MS-NI). After aerobic bicycle training (5×30 min sessions per week) with individualized intensity, no differences were observed between the MS-NI group and the control group. Van den Berg et al. [34] observed the effect of treadmill exercise (4 weeks, 3 days/weeks), reporting that the FSS change not statistically significant. The effect of resistance training on MS fatigue has been investigated in a few studies [26]. Resistance progressive training delivered in a physiotherapy group to reduce fatigue in people with moderate MS (EDSS: 3–5.5) after a 12-week program [35] showed good

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results, as did using aerobic training combined with resistance training on the influence of fatigue [26,28].

The Kargarfed et al. [36] demonstrated benefit in reducing fatigue after completing exercises in water, with patient selection limited to EDSS ≤3.5. The intervention consisted of 8 weeks of supervised aquatic exercise in a swimming pool (3 times a week, each session lasting 60 min). The findings suggest that aquatic exercise training can effectively improve fatigue and HRQOL of patients with MS [36].

Zálišová et al. [37] examined the impact of a physiotherapy program on the condition, fatigue, and general health of MS patients, comparing a control and experimental group of MS patients with similar symptoms and fatigue levels. The experimental group completed the comprehensive rehabilitation program within 6 weeks, with individual therapy aimed at improving overall fitness and reducing fatigue and the effect on individual symptoms. A short warm-up was followed by a section devoted to the endurance load. The subjects were loaded at 60% $VO_{2MAX.}$. Within 6 weeks, the load was increased from 1 min to 10 min. Individual therapy was carried out using physiotherapy techniques on a neurophysiological basis. Group therapy was focused on breathing exercises, autogenous training, and active imagination. The results of the study demonstrated that rehabilitation in the experimental group had a positive impact on cardiorespiratory fitness, fatigue, and the general state of the subjects. Similarly, our study demonstrates that short-term outpatient rehabilitation treatment changes the level of fatigue and confirms the effectiveness of an individualized rehabilitation program.

Our study focused on assessing the impact of physical activity on the perception of fatigue in patients with severe mobility disability. Our data show that an individualized rehabilitation program focused on individual patient issues can positively affect fatigue in patients with MS regardless of disability degrees. Similarly, Judica et al. [4] assessed whether an intensive, short-term inpatient rehabilitation program is able to improve fatigue in MS patients, and if fatigue is able to negatively influence the clinical and functional outcome of rehabilitation in MS. They assessed fatigue symptoms measured with the Fatigue Severity Scale (FSS) before and after rehabilitation, and classified patients into fatigued (FMS) in the case of an FSS score ≥36 and into non-fatigued MS (NFMS) in the case of an FSS <36. Expanded Disability Status Scale (EDSS) and Functional Independence Measure (FIM) were used as clinical outcome measures of the efficacy of the rehabilitation program. They concluded that an intensive, short-term rehabilitation treatment is able to significantly reduce fatigue symptoms in patients with moderate and severe disability compared to untreated MS patients ($p<0.0001$) [4]. Edwards et al. [38] concluded that there is evidence for the benefits of exercise training in persons with MS. However, these benefits have primarily been established in individuals with mild-to-moderate disability (EDSS scores 1.0–5.5), rather than among those with significant mobility impairment. Further, the approaches to exercise training that have been effective in persons with mild-to-moderate MS disability may not be physically accessible for individuals with mobility limitations. The authors suggested that there is need for evidence based on the benefits of physically accessible exercise training approaches for adults with MS with severe mobility disability.

Our study has limitations due to the nature of the disease. Multiple sclerosis is a progressive disease with a varied neurological spectrum. Each patient has a unique clinical situation and the course of the disorder develops over time. Research is influenced by the disunity, heterogeneity, and complexity of the disease itself. Another problematic point of the research was the influence of monitored parameters based on subjective assessment of the patient's mental well-being. The rehabilitation of MS patients has its own specificities. Establishing one program for all patients would be limited to a narrow sample of patients with a similar clinical picture. The provided rehabilitation program must therefore be highly adaptable, requiring highly skilled personnel with knowledge of many physiotherapeutic methods and procedures. The program used in this study was focused on the individual needs of the patient. There is a certain deficiency in the low number of patients in dividing the monitored set with the group according to the EDSS category, so it is appropriate to continue to perform similar studies.

Conclusions

For many years, people with MS have limited their physical activity because of the fear of increased disability. Fatigue is a major symptom affecting the normal daily activities of these patients. This study shows that an individualized rehabilitation program can improve fatigue level in patients with multiple sclerosis, regardless of the disability level. These benefits, although clinically significant, are short-lived; therefore, ongoing physiotherapy might be necessary for sustained benefit, whether this is defined as improvement in mobility or prevention of deterioration. It is thus necessary to ensure the availability of comprehensive outpatient rehabilitation for all MS patients.

Acknowledgments

The research was conducted in cooperation with the Slovak Association of Multiple Sclerosis and Center for the Treatment and Diagnosis of Multiple Sclerosis of J.A. Reiman Hospital in Prešov, Slovakia.

Conflicts of interest

None.

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