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Whole-body cryostimulation (cryotherapy) provides benefits for fatigue and functional status in multiple sclerosis patients. A case–control study

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Objectives – To study the effects of whole-body cryostimulation (WBC) on fatigue and functional status in multiple sclerosis (MS) patients with different levels of fatigue. *Subjects and methods* – Two groups of 24 MS patients with fatigue were studied. At the beginning of the study, the first group presented a Fatigue Severity Scale (FSS) score between 38 and 42 (low-fatigue (LF) group), and the second group had an FSS score between 48 and 52 (high-fatigue (HF) group). Both groups were matched for age and sex. All patients were exposed to 10.3-min session of WBC (one exposure per day at −110°C or lower). Functional status was assessed before and after the series of WBC exposures using the Rivermead Motor Assessment (RMA), the Multiple Sclerosis Impact Scale (MSIS-29), and the Expanded Disability Status Scale (EDSS). The RMA was estimated in three sections: gross function (RMA1), leg and trunk (RMA2), and arm (RMA3). MSIS-29 consists of two subscales assessing the physical (MSIS-29-PHYS) and psychological (MSIS-29-PSYCH) status. *Results* – In both groups, the WBC sessions induced a significant improvement in the functional status and in the feeling of fatigue. However, the changes observed in HF patients were significantly greater than those observed in LF patients, especially in the MSIS-29-PHYS, MSIS-29-PSYCH, RMA1, and RMA3. The changes observed in the EDSS, RMA2, and FSS were similar in both groups. *Conclusions* – WBC appears to be effective in improving functional status and the feeling of fatigue in patients with MS and especially in those who are the most fatigued.

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Key words: fatigue; functional status; multiple sclerosis; quality of life; rehabilitation; whole-body cryostimulation; whole-body cryotherapy

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Introduction

Multiple sclerosis (MS) is a chronic heterogeneous disease with an unpredictable clinical course. This disease presents a wide range of symptoms, such as paralysis, ataxia, spasticity, incontinence, and fatigue syndrome. Fatigue is reported to occur in 70–80% of patients and is considered to be one of the most prevalent and disabling symptoms at all stages of the illness (1). This special kind of lassitude in patients with multiple sclerosis is also called MS-related fatigue and affects a person's social, physical, and occupational well-being (2). The occurrence of the symptoms is daily. The symptoms worsen as the day progress, also with heat and humidity and they significantly interfere with daily functioning. However, fatigue is not related to the level of disability or to mental disorder.

One of the key points in MS treatment should, therefore, be the reduction of fatigue and the facilitation of normal activities in social and

occupational life. However, the control of chronic symptoms, such as fatigue, is not part of the current MS treatment. Globally, disease-modifying drugs have mostly failed as treatments for progressive MS. The standard neurological treatment for MS is focused on reducing the frequency of clinical relapses and new lesion formations. In standard neurological fatigue treatment, amantadine, modafinil, and 4-aminopyridine, often concomitant with antidepressants, are used (3). Obstacles with these pharmacological strategies include a pathogenesis that is not entirely known, some difficulties in precise fatigue estimation, and problems with optimal drug delivery to the CNS due to the brain–blood barrier. Recently, non-pharmacological strategies have been taken into consideration for the treatment patients with of MS, for example, physical exercise (aerobic work), energy conservation strategies, and cognitive behavioral therapy. In practice, a mix of pharmacological and non-pharmacological therapies tailored to the patient's needs are commonly used (4–9).

A unique aspect of patients with MS is their sensitivity to increased body temperature. It is estimated that 60–80% of the MS population experiences a transient and temporary worsening of clinical signs and neurological symptoms as a result of elevated body temperature (10). MS patients with fatigue syndrome seem to be especially sensitive when exposed to heat stress (11). In this context, cooling therapies have been shown to induce positive effects on the functional and mental status of patients with MS (12–14).

Whole-body cryostimulation (WBC) is one mode of cold therapy, during which patients are exposed to very cold air (−110°C or lower) in minimal clothing (a bathing suit, cap, gloves, socks, shoes, and a surgical facemask). It is mainly used to alleviate fatigue, inflammation, and pain in the context of physical recovery after strenuous physical exercise and in the context of numerous disorders (e.g., arthritis, osteoarthritis, fibromyalgia, depression) (15–17).

Recently, we have shown a significant and positive impact of a series of 10 sessions of WBC in MS patients with neurological deficits (muscle strength increase, decreased spasticity, disability reduction, and a higher level of antioxidative status) (18–22). However, the impact of WBC on functional status (physical and psychological aspects) and quality of life in MS patients with fatigue syndrome is unknown (23).

Therefore, the aim of our study was to determine the effects of WBC on fatigue, disability, and physical, functional, and psychological status in selected patients with MS in the progressive stage of the disease with different levels of fatigue.

Methods

The examination enrolled 72 randomized patients with MS at the Neurorehabilitation Ward III General Hospital of Lodz, Poland (Fig. 1). Prior to the study, all of the subjects underwent medical evaluations, including neurological and internal examinations. Inclusion criteria for this study were a diagnosis of MS according to the McDonald criteria, the ability to ambulate independently, and a Fatigue Severity Scale score >38. Moreover, our patients did not use drugs for fatigue therapy (such as amantadine, aminopyridine, or modafinil) to avoid the possible interferences with the antifatigue effects of WBC. Exclusion criteria were the presence of fever, infection, or a relapse and the use of corticosteroids within the past 3 months. Patients were excluded if they had used antihypertensive or vasoactive medications or diuretics within the previous month, or if they had other significant medical diagnoses, including thyroid, hypothalamic, or cardiovascular disease. Patients suffering from circulatory or breathing insufficiency, clotting, embolisms, inflammation of blood vessels, open wounds, ulcers, serious cognitive disturbances, fever, addictions, claustrophobia, or over-sensitivity to cold were excluded from the study. Patients with MS needed to be without any clinical attacks or worsening symptoms over the last 5 years. All eligible subjects received verbal and written information and provided written consent to participate in the study. The protocol and procedures were followed according to the Helsinki Declaration and were approved by Ethics Committee of the Medical University of Lodz, Poland, RNN/260/08/KB. During the course of the study, 24 patients with MS were excluded (13 patients had a common cold and 11 did not completed the entire study).

Data for fatigue were collected using the Fatigue Severity Scale (FSS). This is a widely validated tool consisting of nine fatigue-related statements rated on a seven-point scale (disagree to agree). We used a cutoff value of 38 as suggested by Flachenecker et al. (24) to include only fatigued patients. Patients with MS were further divided into two subgroups depending on their level of fatigue. The first group presented at the beginning of the study an FSS score between 38 and 42 (low-fatigue (LF) group), and the second group had an FSS score between 48 and 52

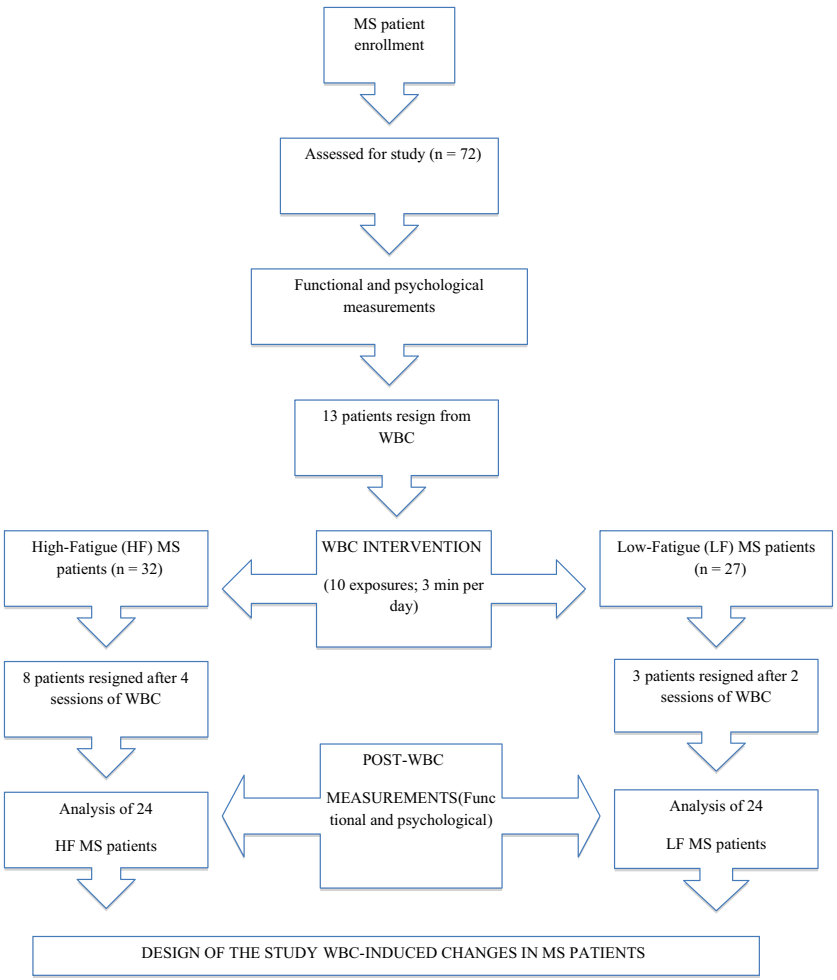

Figure 1. Diagram of the study.

(high-fatigue (HF) group). Both groups were matched for age and sex. There were 14 females and 10 males in each group that completed the entire study. Both groups are described in Table 1.

Functional state was assessed using the Rivermead Motor Assessment (RMA), which consists of three sections: gross function (RMA1), leg and trunk (RMA2), and arm (RMA3); the Expanded Disability Status Scale (EDSS) (25); and the Multiple Sclerosis Impact Scale (MSIS-29) (26). The EDSS is the most commonly used scale for the assessment of impairment and disability. The MSIS-29 consists of two components: physical impact with 20 questions and psychological impact with nine questions; a combined score can be generated, or both components can be reported separately (26).

Both groups were examined at two stages: 1 h before the first 10-day cycle of therapy and 1 h after the last immersion. First, the patients underwent measurements of oral temperature,

Table 1 Baseline characteristics of fatigued multiple sclerosis patients with high fatigue (HF) and low fatigue (LF) levels

	HF (n = 24)	LF (n = 24)
Age (years)	55.6 ± 4.2	55.7 ± 3.2
Gender (male/female)	10/14	10/14
MS duration (years)	16.6 ± 4.8	17.9 ± 5.5
Muscle relaxants[a] (No. of patients)	18	16
Antidepressant (No. of patients)[b]	5	4
BMI (kg/m^2)	22.0 ± 2.5	21.3 ± 2.6
EDSS	5.1 ± 0.7	5.2 ± 1.1
MSIS-29-PHYS	46.8 ± 2.8	45.9 ± 3.2
MSIS-29-PSYCH	42.1 ± 2.7	42.2 ± 2.6
RMA1	7.9 ± 2.2	8.5 ± 2.1
RMA2	6.7 ± 2.3	7.3 ± 1.6
RMA3	9.1 ± 1.7	8.2 ± 1.3
FSS	49.3 ± 1.1	39.3 ± 1.4*

BMI, body mass index; EDSS, Expanded Disability Status Scale; MSIS-29-PHYS, Multiple Sclerosis Impact Scale with 29 physical items; MSIS-29-PSYCH, Multiple Sclerosis Impact Scale with 29 psychological items; RMA, Rivermead Motor Assessment (1, gross function; 2, leg and trunk; 3, Arm); FSS, Fatigue Severity Scale; *significantly different ($P < 0.05$) from the LF group using Mann–Whitney U-test.

[a]Such as tizanidine and baclofen.

[b]Such as coaxil, sertralina, and fluoxetinum.

oxygen saturation, pulse rate, and blood pressure. Afterward, evaluation on all scales was performed. All evaluations took place in a quiet, dimly lit room with a stable ambient temperature (approximately 25°C).

Sessions of whole-body cryostimulation

Patients with MS were exposed 10 times to WBC (one exposure each day) as previously described (22). This occurred in a cryogenic chamber and was carried out daily from Monday to Friday. The cryogenic chamber (KR2005N, liquid nitrogen as a coolant) has two rooms: the vestibule, with a temperature of −60°C, and the main chamber, with temperatures between −110 and −160°C, with liquid nitrogen as the coolant. Sessions in the chamber lasted 2–3 min according to Gregorowicz and Zagrobelny (27) for adult patients.

The protocol and procedures were performed according to the Helsinki Declaration and were approved by the Ethics Committee of the Medical University of Lodz, Poland. The study was performed in the Neurorehabilitation Division III General Hospital in Lodz, Poland.

Statistical analysis

Mann–Whitney *U*-test was used to compare baseline characteristics of the two groups. Wilcoxon test was used to examine the cold-induced changes within our HF and LF groups, and Mann–Whitney *U*-test was used to investigate whether there were different kinds of changes between the two groups of patients with MS. Moreover, we calculated the mean delta values with their confidence intervals and evaluated the changes adjusted for baseline values using covariance analysis. The effect size of the changes (d), defined as the difference between the mean divided by standard deviation of either group, was calculated using the following formula: $d = (M1\text{-}M2)/[((SD1)^2+(SD2)^2)/2]^{0.5}$ where M is the mean and SD is the standard deviation for the changes in subgroups 1 and 2. We estimated a small difference when the d value was 0.2, a moderate difference when d was approximately 0.5, and a large difference when d was 0.8 or above (28). Spearman correlation was used to assess the relationship between baseline FSS and changes in the different variables studied.

All the results are presented as the mean (±SD), and the limit of significance was set at $P < 0.05$ for all of the analyses.

Results

At baseline, there were no differences (age, EDSS, MSIS-29, and RMA) between the groups (Table 1). The influence of WBC on the examined variables in the two groups, HF and LF, is

Table 2 Influence of whole-body cryostimulation (WBC) on functional capacities in groups of fatigued MS patients with high fatigue (HF) and low fatigue (LF) levels

	HF			LF		
	Before	After	Changes	Before	After	Changes
EDSS (0–10 points)	5.1 ± 0.7	4.8 ± 0.7***	−0.3 ± 0.3^{S} (0.2–0.4)	5.2 ± 1.1	5.0 ± 1.1***	−0.2 ± 0.3^{S} (0.1–0.3)
MSIS-29-PHYS (0–100 points)	46.8 ± 2.8	44.9 ± 2.9***	−1.9 ± 1.4^{L} (1.4–2.3)[a,b]	45.9 ± 3.2	45.2 ± 3.0***	−0.7 ± 0.7^{S} (0.2–1.1)
MSIS-29-PSYCH (0–100 points)	42.1 ± 2.7	39.8 ± 2.0***	−2.3 ± 1.9^{L} (1.8–2.8)[a,b]	42.2 ± 2.6	41.3 ± 2.7***	−0.9 ± 1.0^{S} (0.4–1.4)
RMA1 (0–13 points)	7.9 ± 2.2	9.2 ± 2.0***	1.3 ± 1.0^{L} (0.9–1.5)[a,b]	8.5 ± 2.1	9.0 ± 1.9**	0.5 ± 0.7^{M} (0.2 −0.8)
RMA2 (0–10 points)	6.7 ± 2.4	7.9 ± 2.1***	1.3 ± 1.4^{M} (0.8–1.6)	7.3 ± 1.6	8.1 ± 1.5***	0.8 ± 0.7^{M} (0.4–1.3)
RMA3 (0–15 points)	9.1 ± 1.7	11.2 ± 1.5***	2.1 ± 1.1^{L} (1.7–2.6)[a,b]	8.2 ± 1.3	9.0 ± 1.7***	0.8 ± 0.9^{M} (0.3–1.1)
FSS (9–63 points)	49.3 ± 1.1	46.6 ± 1.3***	−2.7 ± 1.6^{L} (2.1–3.3)	39.3 ± 1.4	37.1 ± 1.5***	−2.3 ± 1.3^{L} (1.7–2.8)

'Before' indicated the data collected before the first session of cryostimulation and 'After' the data collected after the series of cryostimulation sessions; **, ***significantly different from the data obtained before cryostimulation (using Wilcoxon test) at $P < 0.01$ and $P < 0.001$, respectively.

[a]Significantly different with the changes observed in the LF group (using Mann–Whitney *U*-test), $P < 0.01$.

[b]Significant difference in the changes adjusted for baseline values using covariance analysis, $P < 0.01$; the letters L, M, and S indicate the size effect of large, moderate, and small, respectively. The results are expressed as their mean and standard deviation, and for the changes, the 95% of the confidence interval is also presented in parentheses. For other abbreviations, see Table 1.

shown in Table 2. Improvements in all the studied tests (EDSS, MSIS-29-PHYS, MSIS-29-PSYCH, RMA1, RMA2, RMA3, and FSS) were found in both groups. However, WBC induced larger changes in the HF than in the LF group in MSIS-29-PHYS, MSIS-29-PSYCH, RMA1, and RMA3. The WBC-induced changes were similar in EDSS, RMA2, and FSS in both groups (Table 2). Positive and significant correlations between baseline FSS and changes (in absolute values) in MSIS-29-PHYS ($r = 0.38$, $P < 0.01$), MSIS-29-PSYCH ($r = 0.42$, $P < 0.01$), RMA1 ($r = 0.32$, $P < 0.05$), RMA3 ($r = 52$, $P < 0.001$), and FSS ($r = 0.32$, $P < 0.05$) were found. There were no statistically significant correlations between initial FSS scores and changes in EDSS and RMA2. No significant correlations were found between age, EDSS at the beginning of the study, or gender vs the WBC-induced changes in the variables investigated in this study.

Discussion

This study compared the effects of WBC in low- and high-fatigue MS patients on functional and psychological outcomes. To the best of our knowledge, this is the first study evaluating both functional and psychological status after WBC in progressive forms of MS. In progressive forms of the disease, patients present a variety of symptoms. Fatigue is one of the most common and difficult symptoms to treat. It should be noted that progressive forms of MS are no longer characterized by clinical attacks and remissions but by insidious progression of clinical symptoms. Relapses with clinical worsening are typical for early stage of MS and last about the first 10 years of the disease (29, 30). Our MS group disease duration was over 10 years. In such chronic disease, novel therapeutic strategies specifically oriented toward improving the quality of life and functional status of patients are necessary (4).

Heat stress presents a significant problem to patients with MS. Conversely, decreasing body temperature may increase the conduction of nerve signaling and may alleviate many symptoms, especially fatigue (31).

Our study shows that regular cold exposure in patients with MS has positive effects on not only the physical but also the psychological status. In the present study, after 10 days of WBC, both groups of patients showed a decrease in the disability score (EDSS). This might be the result of the significant and large fatigue decrease observed in both groups. Moreover, we observed positive changes in functional status in both groups. However, HF patients showed a significantly greater improvement than LF patients in RMA1 and RMA3. Similar improvement occurred in both groups in RMA2.

The critical objective of this study was the evaluation of the impact of WBC on physical and psychological aspects assessed with the MSIS-29 scales. The MSIS-29 is an easy instrument to administer, requiring approximately 5–10 min to complete. The scale is of use for the full range of impairments, disabilities, and handicaps observed in the MS population. The psychometric analysis of MSIS-29-PSYCH and MSIS-29-PHYS revealed the significant impact of WBC in both groups, with a larger effect in the HF group than in the LF group. Moreover, correlations between baseline of FSS and changes in MSIS-29, RMA1, RMA3, and FSS were observed in our study.

Altogether, the effects of WBC were significantly greater in HF than in LF patients. Therefore, WBC appears to be a very useful therapy for all patients with MS and especially for fatigued MS patients. It should be noted that our patients with MS presented moderate level of physical disability (EDSS scores between 3.5 and 6.5).

As MS progresses, the symptomatology develops, and conventional therapy becomes ineffective. It seems that new therapies, especially in the progressive phase of MS, should be more symptom specific. In March 2014, the American Academy of Neurology published the most comprehensive literature review and evidence-based practice guidelines to date for complementary and alternative medical therapies (CAM) for MS (32). In addition to several oral therapies, such as cannabis and ginkgo biloba, it was noted that magnetic fields and reflexology are probably effective for improving fatigue, disability, and quality of life. The first medical studies about thermal sensitivity in MS were published in 1824 and showed that a hot bath-induced numbness in the right leg and reduced feeling and dexterity in the hands of a patient with MS (10). Not only physical but also cognitive impairments and fatigue can be induced by heat exposure in individuals with MS in their routine activities of daily living (10).

Therefore, low temperatures are preferred in MS treatment. Reynolds et al. showed that cooling can improve MS patients' motor skills in the 6-min walk test and the timed up-and-go test, but not in visual acuity or hand grip strength (33).

Recent studies suggest a positive effect of WBC therapy in affective and anxiety disorders,

particularly in depression, which can also occur in patients with MS. The study of Rymaszewska et al. (34) on 26 patients with affective and anxiety disorders showed a statistically significant reduction of 13 from 14 Hamilton Anxiety Rating Scale (HARS) items after 15 exposures of WBC.

In the present study, we noticed that after 10 sessions of WBC, both the HF and LF groups improved significantly in all the variables tested concerning both physical and psychological aspects and fatigue. Overall, the HF group of patients with MS improved significantly more than the LF group. Moreover, the improvement was correlated to the baseline FSS score. In other words, the WBC had a larger impact on the most fatigued patients. As suggested by our previous work, WBC is a novel therapy that might be recommended as an additional treatment in the reduction of fatigue and depression to improve functional abilities and quality of life. However, one limit in our study concerns the lack of information on how long the effects (concerning fatigue and other measured variables) are maintained after WBC. Additional evaluations should be organized at distance from the last session of WBC and information on how much fatigue and other parameters may change in a 2-week period in fatigued MS patients should be obtained. Moreover, in the context of WBC, we have no possibility of conducting blind study which is a clear drawback for conducting clinical studies.

Clinical messages

There is no medication approved specifically to treat MS-related fatigue. WBC therapy appears to be a safe and effective treatment, especially in patients with high FSS scores. WBC is a novel therapy that might be recommended as an additional treatment in patients with MS for the reduction of fatigue to improve functional abilities and quality of life.

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Conflict of interest

The authors declare no conflict of interest.

Author contribution

EM, BD, and JK conceived and designed the experiments. TW, EM, and JK performed the experiments. JK and BD analyzed the data. EM drafted the manuscript. EM oversaw the WBC. All authors read and approved the final manuscript.

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