THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 20, Number 5, 2014, pp. 347–355

DOI: 10.1089/acm.2013.0188

A Multimodal Intervention for Patients with Secondary Progressive Multiple Sclerosis: Feasibility and Effect on Fatigue

Babita Bisht, BPT,[1] Warren G. Darling, PhD,[1] Ruth E. Grossmann, RN, PhD,[2] E. Torage Shivapour, MD,[3] Susan K. Lutgendorf, PhD,[4,5,6] Linda G. Snetselaar, PhD, RD, LD,[7] Michael J. Hall, PhD,[8,9] M. Bridget Zimmerman, PhD,[10] and Terry L. Wahls, MD[11,12]

Abstract

Background: Multiple sclerosis is an autoimmune disease influenced by environmental factors.
Objectives: The feasibility of a multimodal intervention and its effect on perceived fatigue in patients with secondary progressive multiple sclerosis were assessed.
Design/setting: This was a single-arm, open-label intervention study in an outpatient setting.
Interventions: A multimodal intervention including a modified paleolithic diet with supplements, stretching, strengthening exercises with electrical stimulation of trunk and lower limb muscles, meditation, and massage was used.
Outcome measures: Adherence to each component of the intervention was calculated using daily logs. Side-effects were assessed from a monthly questionnaire and blood analyses. Fatigue was assessed using the Fatigue Severity Scale (FSS). Data were collected at baseline and months 1, 2, 3, 6, 9, and 12.
Results: Ten (10) of 13 subjects who were enrolled in a 2-week run-in phase were eligible to continue in the 12-month main study. Of those 10 subjects, 8 completed the study and 6 subjects fully adhered to the study intervention for 12 months. Over a 12-month period, average adherence to diet exceeded 90% of days, and to exercise/muscle stimulation exceeded 75% of days. Nutritional supplements intake varied among and within subjects. Group daily average duration of meditation was 13.3 minutes and of massage was 7.2 minutes. No adverse side-effects were reported. Group average FSS scores decreased from 5.7 at baseline to 3.32 ($p = 0.0008$) at 12 months.
Conclusions: In this small, uncontrolled pilot study, there was a significant improvement in fatigue in those who completed the study. Given the small sample size and completer rate, further evaluation of this multimodal therapy is warranted.

Introduction

Multiple sclerosis (MS) is an immune-mediated disease influenced by the interaction of genetics and environmental factors.[1,2] There is increasing interest in the development of combination therapies, using immune suppressants and drugs with distinct mechanisms of action, but side-effects limit the number of pharmacologic agents that can be safely used.[3–5] Combinations of nonpharmaceutical treatments that are known to increase muscle strength and

[1]Department of Health and Human Physiology, University of Iowa College of Liberal Arts and Sciences, University of Iowa, Iowa City, IA.
[2]College of Nursing, University of Iowa, Iowa City, IA.
[3]Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, IA.
[4]Department of Psychology, College of Liberal Arts and Sciences, University of Iowa, Iowa City, IA.
[5]Departments of Obstetrics and Gynecology and [6]Urology, Carver College of Medicine, University of Iowa, Iowa City, IA.
[7]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA.
[8]Department of Psychiatry, VA Medical Center, Iowa City, IA.
[9]Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City, IA.
[10]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA.
[11]Department of Internal Medicine, Veterans Administration Medical Center, Iowa City, IA.
[12]Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, IA.

positively influence brain function by multiple mechanisms of action but with minimal side-effects may provide an alternative treatment.[6]

Progressive muscle weakness and fatigue are the chief complaints of MS patients and lead to decreased physical activity and disability. Performing a progressive exercise program (PEP) would be expected to improve function of secondary progressive multiple sclerosis (SPMS) patients[7] but a recent meta-analysis showed that the effects of exercise for up to three months are usually modest.[8] Neuromuscular electrical stimulation (NMES) may also provide benefits by increasing muscle activation during exercises and reducing spasticity. Such stimulation is Food and Drug Administration (FDA)–approved for treating muscle pain and spasm and for reducing muscle atrophy, all of which are typical in SPMS. Both exercise and electrical stimulation are associated with increased nerve-growth factors including brain-derived neurotrophic factor, insulin-like growth factor, glial cell growth factor, and endorphins,[9,10] which are all critical for repair of myelin and are diminished in SPMS. Exercise and NMES may synergize to produce a better treatment for SPMS than either alone.

Nutritional status has a major impact on cognitive function and brain volume in healthy individuals[11] and is likely even more important in people with SPMS.[12,13] The number of mean daily servings of vegetables is inversely correlated with the risk of developing MS and obesity,[14] a common comorbidity.[1] Greens, sulfur-rich vegetables and brightly colored vegetables provide many dietary molecules (e.g., flavonoids, polyphenols, and thiols) with favorable impact on molecular pathways influencing MS disease activity (e.g., sirtuins, adenosine monophosphate protein kinase, nuclear transcription factor κ B, and peroxime proliferator-activated receptors)[12,13] and nutrients important to optimal brain physiology.[11,15,16]

Currently, no particular diet is prescribed as a treatment for MS, but some studies suggest that changes in diet might be beneficial. For example, the Swank diet, which is low in saturated fat, reduces the progression of disability and mortality rate in patients with relapsing–remitting MS.[17,18] In 2009, a case report of a patient with SPMS (TW) showed that a modified paleolithic diet (see Table 1 for a detailed description), consisting mainly of greens, sulfur-containing vegetables and colored fruits and vegetables and elimination of gluten, dairy, and eggs enhanced the recovery of this patient and led to improvement in fatigue and transition from wheelchair dependence to mild gait disability.[19] This individual (TW) was receiving physical therapy and NMES before adding the diet to her intervention, suggesting beneficial effects of a combination of treatments. Moreover, a case series assessing effects of PEP + NMES in six patients with SPMS or primary progressive MS demonstrated increased mobility, including reduced need for assistive devices.[20] On the basis of these reports, the effects of a multimodal intervention including the modified paleolithic diet, PEP, NMES, and stress-reduction techniques were investigated in subjects with SPMS. To investigate the feasibility of treating SPMS with multiple interventions, an assessment was done of subjects' adherence to three main components (diet, PEP, and NMES) of this multimodal intervention and its effect on perceived fatigue. It was hypothesized that SPMS subjects would be able to adopt and sustain multiple interventions with minimal side-effects and that the multimodal intervention would decrease perceived fatigue. The clinical trials protocol registration number is NCT01381354.

Materials and Methods

In this one-arm feasibility study, the inclusion criteria were as follows: diagnosis of SPMS confirmed by the study neurologist (E.T.S.) based on subject's medical history, clinical presentation, brain and spinal magnetic resonance imaging (MRI) and spinal fluid examination; age 18–65 years; some level of gait impairment but ability to walk 25 feet with or without an assistive device (as confirmed by subject during screening questions); and an adult companion willing to assist with home exercise and NMES. The exclusion criteria were the following: change in MS status in prior 3 months, abnormal renal or hepatic functions, active cancer, psychotic disorder, significant cognitive dysfunction, seizure disorder, heart block or abnormal rhythm, unstable heart disease, lung disease or diabetes requiring change in medication in prior 3 months, any implanted

Table 1. Study Diet Developed by T. Wahls

Food item	*Instruction*	*Recommended daily intake*
Green leafy vegetables	Recommended[a]	3 cups cooked/6 cups raw = 3 servings
Sulfur-rich vegetables	Recommended[a]	3 cups raw or cooked = 3 servings
Intensely colored fruits or vegetables	Recommended[a]	3 cups raw or cooked = 3 servings
Omega-3 oils	Encouraged	2 tablespoons
Animal protein	Encouraged	4 ounces or more
Plant protein	Encouraged	4 ounces or more
Nutritional yeast	Encouraged	1 tablespoon
Milks: soy, almond, peanut, rice, and coconut	Encouraged	According to subject choice
Kelp	Encouraged	¼ teaspoon powder or 2 capsules
Spirulina/chlorella/klamath blue–green algae	Encouraged	¼ to 1 teaspoon or 4 to 8 capsules
Gluten-free grains/starchy food	Allowed	Only two servings per week
Gluten-containing grain	Excluded	
Dairy	Excluded	
Eggs	Excluded	

[a]If not able to take total nine servings of recommended food, subjects were asked to take equal proportion of each category.

electronic device, antiplatelet or blood thinner medication and 25(OH)D >150 ng/mL or >100 ng/mL with an abnormal elevation of blood calcium (>10.2 mg/dL). This study was approved by the University of Iowa Institutional Review Board, and informed consent was obtained for all subjects.

Intervention

Run-in phase. On initial enrollment, subjects were instructed to follow the study diet (Table 1) and a stretching program at home for 2 weeks to confirm participant willingness to adopt the study interventions. The study diet was a modified paleolithic diet consisting of recommended foods (green leafy vegetables, sulfur-containing vegetables, and intensely colored fruits and vegetables), encouraged foods (plant and animal protein, seaweed, nondairy milks), and excluded foods (gluten-containing grains, eggs, and dairy). To facilitate adherence with this diet, subjects were provided with menus and recipes. The stretching program focused on gastrocsoleus, hamstrings, gluteus maximus, and erector spinae muscles. Each subject's adult companion was instructed to assist during stretching exercises. Subjects were called twice during the run-in phase by research assistants to answer questions regarding diet and stretching program. To be eligible for the 12-month main study, subjects had to show adherence to study diet (daily intake of recommended foods and avoidance of excluded foods) for 7 consecutive days during a 2-week run-in phase.

Main study. After enrollment into the main study, an exercise–NMES program, optional nutritional supplements (see Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/acm), and stress-reduction techniques were added to the run-in intervention. Potential side-effects of each supplement were described in the consent form. Subjects could opt not to take a supplement for any reason. Subjects were instructed to add one supplement every other day and discontinue intake if any side-effect was perceived. For stress reduction, subjects were instructed to do meditation and self-massage of hands, feet, and face. A session of mindfulness meditation emphasizing concentration on breathing (as suggested in Institute of Functional Medicine toolkit, 2010)[21] was conducted. Subjects could use any other method of meditation as well. Twenty (20) minutes of daily stress reduction was recommended. The exercise–NMES program consisted of strengthening exercises of leg and trunk muscles with accompanying NMES (Table 2). Strength of dorsiflexors, quadriceps, hamstrings, gluteus maximus, abdominals, and erector spinae muscles was assessed using manual muscle testing (MMT). Type and repetitions of exercises were recommended to each subject based on her/his muscle strength in particular muscle groups. NMES was applied on all weak muscles (i.e., <7/10 on MMT) even if subjects were not able to perform exercise of that muscle. Electrical stimulation was applied with a portable NMES device (EMPI 300 PV) using program 6 (80 Hz, 300 μs, 10 seconds on, 5 seconds off, 2-second ramp up, 2-second ramp down). Subjects and adult companions were instructed on proper application of electrical stimulation to the muscles and how to perform strengthening exercises during NMES. To begin, subjects were asked to perform 10–20 repetitions of exercise of a muscle group within 10 minutes of electrical stimulation, thus giving them time to perform exercises with stimulation and rest between repetitions. Intensity of NMES was controlled by subjects and was recommended to remain within a comfortable level. Subjects were asked to perform stretches and an exercise–NMES program at least 5 days/week. In addition, optional use of program 1 (for large-muscle groups, 35 Hz, 300 μs) and program 2 (for small-muscle groups, 45 Hz, 300 μs) at submotor intensity (to generate a tingling sensation but no muscle contraction) was also recommended during activities of daily living. Number of daily repetitions of stretches and strengthening exercises and total duration of electrical stimulation were progressively increased as the subject's tolerance improved. Research assistants called the subjects weekly in the first 2 months to answer any questions related to the intervention. Also, subjects called the study team if they had any questions about any part of the intervention during the study period. Motivational interviewing techniques such as use of open-ended questions and reflective statements were used by research assistants while talking to subjects to improve and sustain adherence with interventions.[22]

Table 2. Recommended Exercises and Muscles Stimulated During Particular Exercise

Exercise	*Muscle stimulated during the exercise*
Pelvic tilt Crunches	Abdominals
Right-angle bridge Hip abduction Hip abduction & extension	Gluteus maximus
Bridging Walking bridge Hunter dog	Erector spinae
Wall slides	No NMES

NMES, neuromuscular electrical stimulation.

Outcome measures. Primary outcome measures were (1) adherence to study diet and exercise–NMES program, (2) side-effects of the intervention, and (3) perceived fatigue. Adherence to study interventions and perceived fatigue were measured at 3, 6, 9, and 12 months, whereas side-effects were assessed at 1, 2, 3, 6, 9, and 12 months after starting the intervention. Secondary outcome measures included (1) average daily intake of each food category, (2) type and daily dosage of nutritional supplements, average total daily minutes of: (3) NMES with programs 1 and 2, and (4) meditation and massage. Subjects were asked to keep daily records of their food intake, type, and repetitions of each exercise performed and total duration of electrical stimulation applied during a 12-month intervention period. Adherence with diet and an exercise–NMES program was calculated as percentage of the days subjects filled in the daily logs showing that they consumed any of the recommended foods and did not consume any excluded food (considered adherent to the diet). Due to variation in subject's weight, precise serving sizes were not considered for adherence, and subjects were asked to eat recommended foods according to their appetite. Adherence to

the exercise–NMES program was considered full in a day if subject performed strengthening exercises or NMES or both. Potential side-effects were assessed from monthly questionnaires and blood analyses (complete blood count test, creatinine, calcium, magnesium, and alanine aminotransferase, conducted at Iowa City Veteran Affairs Medical Center). Subjects were asked to indicate if they perceived any side-effects such as diarrhea, bloating, bruising, etc. and if so, how would they rate it (mild, moderate, or severe). Information regarding burns and discomfort associated with NMES were also asked in the questionnaire. Perceived fatigue was assessed using the FSS. Subject's daily logs and monthly side-effects questionnaires were collected at their 1, 2, 3, 6, 9, and 12-month visits. Blood analyses were performed at 1, 3, 6, 9, and 12-month visits.

Statistical analysis. Linear mixed model for repeated measures[23] was used for assessing adherence with diet and the exercise–NMES program and its effect on perceived fatigue at 3, 6, 9, and 12 months after starting the intervention. All available data were used under the assumption of data missing at random. When appropriate, the Dunnett–Hsu[24] test was used for post-hoc comparisons.

Results

Subjects

Thirteen (13) subjects with SPMS (of 34 screened) were enrolled in the run-in phase; 10 of these subjects were eligible for the 12-month main study. One subject (S10) dropped out of the study within 3 months due to unknown reasons. Thus, postintervention data of only nine subjects have been reported. One subject's (S8) participation was terminated at 6 months due to clinically significant cognitive decline. Thus, eight subjects continued their participation for 12 months. Although, subject 6 (S6) participated in the study for 12 months, her data were excluded from adherence analysis due to false reporting in daily logs (as mentioned by the subject herself). Subjects' enrollment and follow-up during the study are shown in Figure 1. Baseline characteristics of subjects are shown in Table 3.

Study diet and nutritional supplements. Subjects completed diet logs for an average of 90 days (96%) between visits. Group average adherent days averaged over 90% at 3, 6, 9, and 12 months (Fig. 2: Grp). No significant change in mean diet adherence at different time points occurred ($p = 0.45$). Adherence varied from nearly full (>90%) (Fig. 2: S1, S3, S5, S9, S14) to lower adherence that varied with duration of intervention (e.g., Fig. 2: S2, S11). Subject 2 (S2) decreased adherence after 6 months for personal reasons (severe family stress). She did not adhere to diet (as mentioned by subject) and did not fill in logs between 9- and 12-month visits. Group average daily intake of recommended food was 1.8 servings at baseline and increased to 7.1, 6.8, 6.2, and 6.4 servings at 3, 6, 9, and 12 months, respectively (Supplementary Fig. S1). Although subjects were asked to eat each category of recommended food items in equal proportion, they ate colored fruits and vegetables more frequently than other categories (1.4:1.0:1.2 daily servings of colors, sulfur, and greens, respectively). Group average daily intake of excluded food decreased from 4.9 servings at baseline to 0.05, 0.05, 0.1, and 0.1 servings at 3, 6, 9, and 12 months, respectively. On average, subjects reported minimal intake of excluded foods ranging from 0 to 0.2 servings per day during a 12-months period except subject S2, who resumed eating excluded food after 6 months and reported an average of 0.6 servings/day at 9 months. Nutritional supplement regimen varied among and within subjects at different time points during the study. Resveratrol was withdrawn from the supplement regimen during the study due to FDA concern about resveratrol use in an unrelated study.

Stretching program. On average more than six daily stretches of each muscle group were performed (Supplementary Fig. S2). Number of stretches varied among subjects and with time. S5 and S8 were severely disabled from baseline and experienced worsening of symptoms within 3 months into the study, which led to a decrease in number of stretches performed over time and high variability in the group average.

Exercises and NMES program. Subjects completed exercise–NMES logs for average 90 days (96%) between visits. Subjects performed either exercise or NMES for more than 75% of days (Fig. 3: Grp) and both exercise and NMES on more than 60% of days. No significant change in mean exercise–NMES adherence at different time points occurred ($p = 0.65$). Adherence with the exercise–NMES program varied from nearly full (>70% or 5 days/week) (Fig. 3: S3, S8, S9, S11) to low adherence that varied with duration of intervention (e.g., Fig. 3: S1, S2, S5, S14). Average daily repetitions of strengthening exercises (Supplementary Table S2) and total duration of NMES with program 6 (Supplementary Fig. S3) and program 1 or 2 (Supplementary Table S3) varied among subjects and with time. Subjects performed exercise depending on their capability and assistance available. Thus, total number of daily exercise repetitions varied from 140 (S11) to almost none (S8). Similarly, high variation in duration of NMES was reported ranging from 5 minutes to 50 minutes of NMES on each muscle group. Some subjects also performed additional strengthening exercises (e.g., for dorsiflexors and hamstrings).

Meditation and massage. Average daily duration of meditation was 18.7, 13.9, 10.1, and 10.6 minutes at 3, 6, 9, and 12 months, respectively (Supplementary Table S4A). Average daily duration of massage was 9, 7, 7.4, and 5.6 minutes at 3, 6, 9, and 12 months, respectively (Supplementary Table S4B).

Side-effects. No serious adverse events were reported. Mild-to-moderate gastrointestinal side-effects following use of supplements were reported and were resolved in all cases by either decreasing the dosage or stopping the particular supplement. S5 and S11 reported one minor skin burn, and S3 reported minor skin burns twice following NMES. These subjects were instructed to not apply stimulation on the burnt area until healed properly and to keep the current intensity within a comfortable level. S2 and S9 reported headaches with high intensity of stimulation, which was resolved by decreasing current intensity. Safety blood analyses remained within normal limits for all subjects except S1, whose alanine aminotransferase was higher than normal

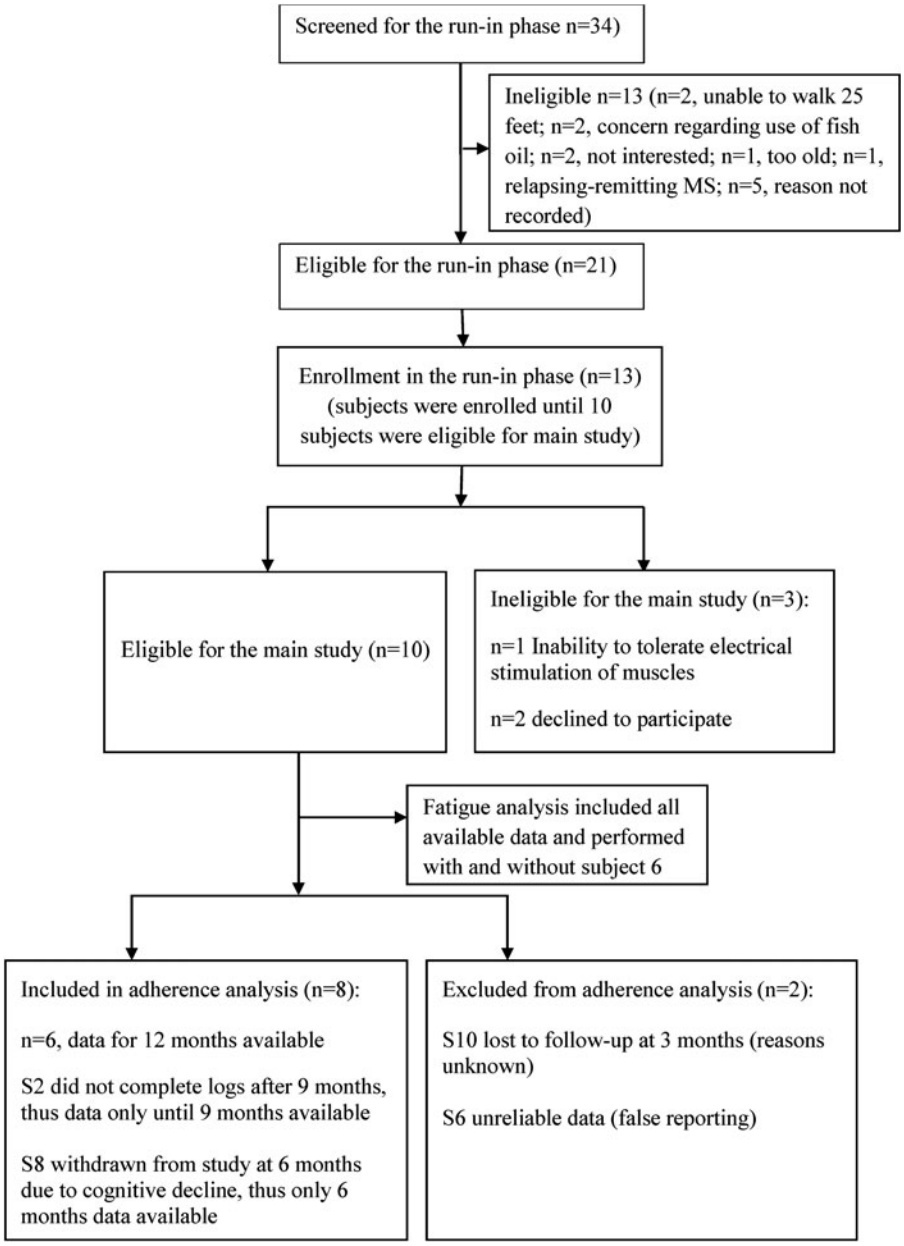

FIG. 1. Flow diagram of subject enrollment, eligibility, and follow-up during 12 months.

at 3 months but decreased to the normal range during subsequent visits.

Overweight and obese subjects showed significant weight loss ($\geq 10\%$ from baseline; Table 4: S1, S5, S9, S11). S5 exhibited the greatest loss from baseline (23.9%) and was diagnosed with chronic leukemia (attributed to the prior use of mitoxantrone for SPMS) after the 12-month visit, which was judged to be the likely cause of her weight loss. To prevent excessive weight loss, subjects were instructed to increase intake of animal protein and coconut oil. The subject's primary-care doctors were informed if they lost more than 10% of baseline weight at 6 months. The group average percentage decrease in body–mass index (BMI) during a 12-month period was 7.7% (range: $+1.8$ to -23.9%) kg/m^2. All subjects maintained BMI > 18.5 kg/m^2 throughout the study period.

Perceived fatigue. Seven (7) of nine subjects exhibited decreased FSS scores over the study period (Fig. 4). Significant reductions in average FSS scores at each time point were observed including ($F_{4,30.2} = 11.8$, $p < 0.001$) and excluding ($F_{4,26.3} = 11.8$, $p < 0.001$) data of subject 6. Dunnett-Hsu post-hoc test showed significant decreases in average FSS scores by: 1.8 ($p = < 0.0001$), 1.6 ($p = 0.0007$), 2.1 ($p = 0.0002$) and 2.3 ($p = 0.0004$) points from baseline at 3, 6, 9, and 12 months, respectively, when subject 6 was included (Fig. 4: Grp), and results were similar when subject 6 was excluded (average FSS scores decreased by: 1.7 [$p = < 0.0001$], 1.5 [$p = 0.003$], 2.1 [$p = 0.0009$], and 2.4 [$p = 0.0008$] points from baseline at 3, 6, 9, and 12 months, respectively).

Discussion

The present study represents a significant advance in study of potential alternative therapies for SPMS. Results of this study suggest that it is challenging to adhere to multimodal intervention, as only 77% (10/13) of carefully

Table 3. Baseline Characteristics of the Subjects in the Main Study

Subject ID	*Age (years)*	*Sex/race*	*Years since MS diagnosis*	*EDSS at baseline*	*Baseline BMI (kg/m^2)*	*Highest education*	*Comorbid diagnosis*	*Disease-modifying drugs*[a]
S1	45.6	F/C	10	6	29	High school		R
S2	53.8	F/C	14	6	21.8	Some college	MO	
S3	54.2	F/C	20	6.5	20	Master's	O, Cat, UC	
S5	57.3	F/C	11	6.5	30	Master's	HBP	Av
S6	52.5	F/C	3	6	20	Some college	A	
S8	55.2	F/C	35	6.5	32.8	Master's		
S9	52.2	F/C	25	6	26.5	2-year Associate	O, HBP, Ch	Cop
S11	54.8	F/C	11	6	27.2	4-year Bachelor's		
S14	45.9	M/H	13	6.5	22.3	Professional degree (MD)		B
Mean	52.4		15.8	6.2	25.5			
SD	4.1		9.5	0.3	4.7			

S1 stopped taking rebif during the study.

[a]Subjects chose to take disease-modifying drugs although they understood that disease modifying drugs are not considered effective therapy for secondary progressive multiple sclerosis.

Av, avonex; B, betaseron; BMI, body–mass index; C, Caucasian; UC, uterine cancer; Cat, cataract; Ch, high cholesterol; Cop, copaxon; EDSS, expanded disability status score; F, female; H, Hispanic; HBP, high blood pressure; M, male; MO, mood problem; MS, multiple sclerosis; O, osteoporosis; R, rebif; SD, standard deviation.

screened subjects could continue participation beyond run-in phase and only 60% (6/10) of these subjects continued adherence with such intervention for 12 months. However, most subjects (7/9) who followed the intervention reported clinically significant improvements in perceived fatigue.

Several environmental factors including reduced sun exposure, malnutrition, toxin exposure, stress, and reduced physical activity are known to affect the development and course of MS. However, research evaluating the use of multiple interventions to reduce the impact of these environmental factors on MS-related symptoms is sparse. The OPTIMISE study[25] used a multidisciplinary program to encourage health-promoting activities such as physical activity, fatigue and stress management, and nutritional awareness over a period of 8 weeks, which led to significant increases in healthy activities by MS subjects (e.g., the number of subjects performing leisure-time physical activity increased from 6% at baseline to 40% after the program). Thus, when provided with specific information and opportunity to gain skills, subjects with MS can make lifestyle changes.[25] In a similar study of health-behavior promotion, a 5-day residential retreat aimed at promoting lifestyle modification (diet, exercise, and stress-reducing activities) was conducted and demonstrated significant improvement in health-related quality of life at 1 and 5 years.[26] However, adherence of subjects to the intervention was not evaluated. Unlike these aforementioned studies, a more structured diet (instructions about recommended and excluded food) and muscle-specific exercises along with NMES were included in our study, and adherence to the different components of intervention were evaluated over a longer period of time.

Multiple interventions were used to target different symptoms of MS. Given the complexity of the intervention and effort needed to adhere to all of its components, only subjects who had an adult companion to assist them during the study were enrolled. Also, provision of a run-in phase to

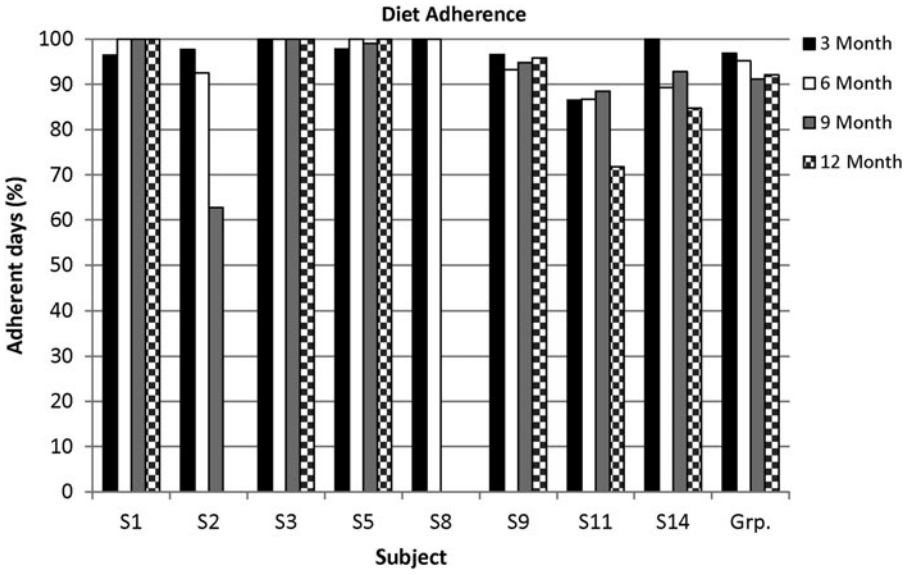

FIG. 2. Average dietary adherence (% adherent days) of each subject and the group (Grp.) at 3, 6, 9, and 12 months. Subject 2 did not complete logs from months 9–12.

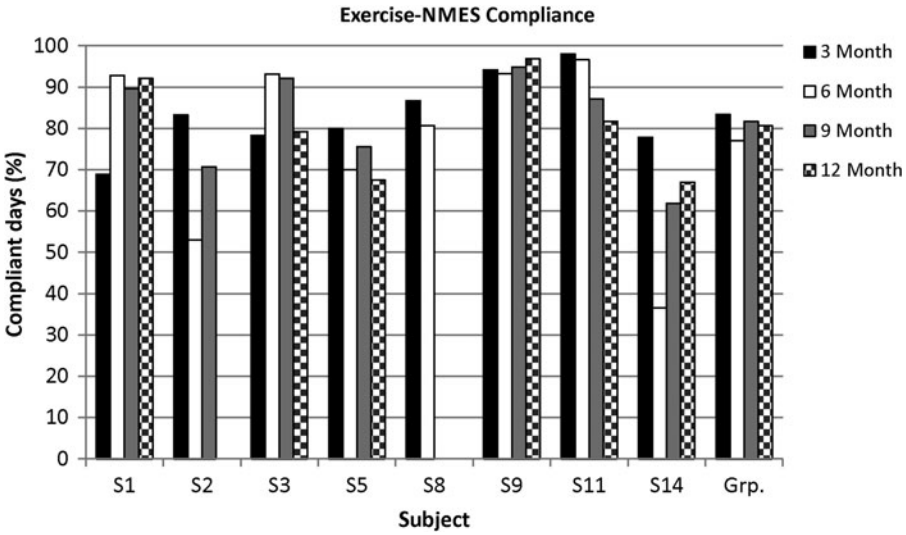

FIG. 3. Average exercise–neuromuscular electrical stimulation (NMES) adherence (% adherent days) of each subject and the group at baseline, 3, 6, 9, and 12 months. Subject 2 did not complete logs from months 9–12.

try the study diet and stretching exercises gave subjects an opportunity to explore the challenge of adhering to the intervention. These factors might have excluded the subjects who either were not motivated or did not have family support to follow such a complex intervention. However, 77% (10/13) of subjects enrolled in the run-in phase continued in the main study, of whom 60% (6/10) showed good adherence with the intervention for 12 months, suggesting that it is difficult to adhere to this multimodal intervention. Notably, lack of family support (one of the exclusion criteria) due to divorce was cited as the reason for decreased adherence by one subject (S2) after 6 months into the study. One subject (S8) was terminated from the study after 6 months due to clinically significant cognitive decline and another subject (S10) dropped out of the study within the first 3 months and gave no specific reason for doing so. Thus, greater adherence might have been shown if these three subjects had family support or disease progression similar to other subjects in the study. Adhering to this multimodal intervention is difficult, especially for severely disabled subjects, because of the demands for food preparation and NMES, which require assistance. On the other hand, subjects who are capable of following this complex intervention are likely to experience reduced perceived fatigue, which is difficult to treat.

Fatigue is one of the most disabling symptoms of MS,[27] but its underlying pathophysiology is poorly understood. A review by Lee et al.[27] suggested that pharmacological (Prokarin [histamine and caffeine], modafinil, etc.) and psychosocial/psychological interventions (yoga, energy conservation, pulsed electromagnetic therapy, etc.) have only modest effect on MS fatigue. Similarly, beneficial effects of exercises on MS fatigue have been reported but findings are inconsistent.[28] In the present study, both statistically and clinically significant (>0.5 points on FSS as reported by Tomassini[29]) improvement in perceived fatigue of seven of nine subjects occurred. These results contrast with those of a randomized controlled study in patients with relapsing–remitting MS (RRMS) that compared the effects of two interventions—(1) naturopathic medicine plus usual care and (2) MS education plus usual care—to a usual-care control group and showed that changes in perceived fatigue were similar among the three groups with none of the groups having significant decreases in fatigue.[30] Differences in

Table 4. Change in Subjects' Weight (kg) During 12 Months

Subject	*Baseline*	*12 month*	*% Change from baseline*
S1	81.4	71	−12.8
S2	64.7	65	0.5
S3	56.4	57.2	1.4
S5	76.3	58.1	−23.9
S6	60.7	56.5	−6.9
S8	80.5	80.5[a]	
S9	69.9	59.9	−14.3
S11	65.4	55.5	−15.1
S14	70.4	71.4	1.4
Group	69.5	63.9	−7.7
SD	8.7	8.7	9.2

[a]At 6 months.
SD, standard deviation.

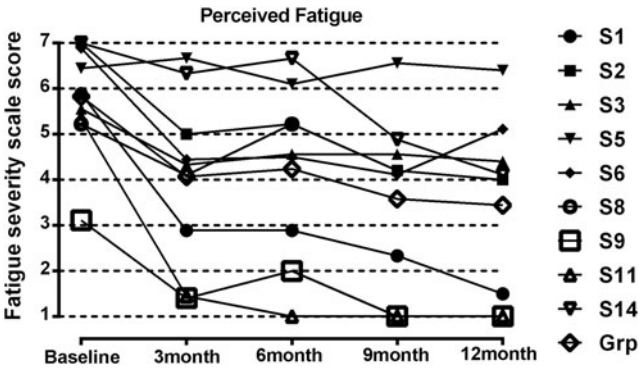

FIG. 4. Perceived fatigue (Fatigue Severity Scale score) of each subject and the group (Grp.) average at baseline, 3, 6, 9, and 12 months.

subject populations (RRMS versus SPMS), intervention, and shorter duration of the intervention of this study likely account for the different findings. To the authors' knowledge, a robust effect on perceived fatigue in MS has not been reported following any individual intervention. The synergistic effects of multiple interventions probably led to a large improvement in fatigue in this study, suggesting that a comprehensive approach is needed to treat MS fatigue.

Limitations of the Study

A small sample size is the primary limitation of this phase 1 pilot study. This was a single-arm, open-label study investigating the effects of a combined intervention in subjects with SPMS. Although lacking a control group, this study was performed in SPMS individuals and previous studies have reported progressive worsening of various symptoms of SPMS subjects in both placebo and treatment groups (e.g., interferon-β) over 6 months.[31–33] Future studies should include a control group to further test the efficacy of this intervention. Another limitation of this study is that standard criteria to diagnose MS were not used for these subjects because the time of their initial diagnosis dated to before these criteria were set. However, diagnosis of a secondary progressive course of MS was confirmed by the study neurologist (E.T.S.), who specializes in treating patients with MS and has several years of experience treating patients with MS. As stated above, the SPMS diagnosis was confirmed based on the subject's medical history, clinical presentation, brain and spinal MRI, and cerebrospinal fluid examination. In addition, multiple therapeutic lifestyle interventions, potentially impacting multiple disease pathways, were simultaneously studied, which makes it difficult to interpret effects of diet versus exercise versus NMES versus stress reduction. However, this study focused on whether subjects would adopt and sustain this combination of interventions and on assessing the potential side-effects, not on the efficacy of the intervention components.

Conclusions

Most subjects with SPMS were able to successfully adopt and sustain a complex lifestyle intervention consisting of a modified paleolithic diet, exercise–NMES, meditation, and massage with minimal side-effects. Importantly, this intervention also showed clinically significant improvement in perceived fatigue of SPMS subjects. Because of space limitations, the outcomes related to changes in quality of life, motor function, mood, cognitive function, and blood biomarkers will be reported in a follow-up report.

Acknowledgments

Catherine Swanson, MD and Catherine A. Chenard, MS, RD, LD supported the project. Student researchers who supported the project are Daniel Klein, Nicole Grogan, Kaitlin White, Emily White, John Bolton, Alejandra Gonzalez, Allison Banwort, Alison Crimson, Danielle Dietz, Emily Bradley, Summer Anderson, Glenda Mutinda, Carl Sohocki, Kyle Suhr, and Owen Sessions. This work was supported by Direct MS Charity of Canada and the Institute for Clinical and Translational Science at the University of Iowa which is supported by the National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program, grant 2 UL1 TR000442-06. The CTSA program is led by the NIH's National Center for Advancing Translational Sciences (NCATS). This publication's contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. In-kind support was provided from DJO Inc., Pinnaclife Inc., and TZ Press LLC. Data used in this article were presented at the 2013 Ancestral Health Symposium, August 15, 2013, Atlanta, GA.

Disclosure Statement

Dr. Terry Wahls has equity interest in the following companies: Dr. Terry Wahls LLC; TZ Press LLC; Xcellerator LLC; RDT LLC; and the website www.terrywahls.com. She also owns the copyright to the book *Minding My Mitochondria, 2nd Edition* and has an application pending for trademark for the Wahls Protocol™, and a patent pending for a therapeutic electrode garment. Dr. Wahls has conflict of interest management plans in place with both the University of Iowa and the Veterans Affairs Iowa City Healthcare System.

References

1. Lauer K. Environmental risk factors in multiple sclerosis. Expert Rev Neurother 2010;10:421–440.
2. Stuve O, Oksenberg J. Multiple sclerosis overview. In: Pagon RA, Bird TD, Dolan CR, et al., eds. GeneReviews. Seattle, WA: University of Washington, Seattle; 1993–2013.
3. Jeffery DR, Chepuri N, Durden D, Burdette J. A pilot trial of combination therapy with mitoxantrone and interferon beta-1b using monthly gadolinium-enhanced magnetic resonance imaging. Multiple Sclerosis. 2005;11:296–301.
4. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. NEJM 2006;354:911–923.
5. Fernandez O, Guerrero M, Mayorga C, et al. Combination therapy with interferon beta-1b and azathioprine in secondary progressive multiple sclerosis: A two-year pilot study. J Neurol 2002;249:1058–1062.
6. Stuart WH. Combination therapy for the treatment of multiple sclerosis: Challenges and opportunities. Curr Med Res Opinion 2007;23:1199–1208.
7. Romberg A, Virtanen A, Ruutiainen J. Long-term exercise improves functional impairment but not quality of life in multiple sclerosis. J Neurol 2005;252:839–845.
8. Snook EM, Motl RW. Effect of exercise training on walking mobility in multiple sclerosis: A meta-analysis. Neurorehab Neural Repair 2009;23:108–116.
9. Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci 2001;21:5678–5684.
10. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: Key roles of growth factor cascades and inflammation. Trends Neurosci 2007;30:464–472.
11. Bowman GL, Silbert LC, Howieson D, et al. Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging. Neurology 2012;78:241–249.
12. Riccio P, Rossano R, Liuzzi GM. May diet and dietary supplements improve the wellness of multiple sclerosis patients? A molecular approach. Autoimmune Dis 2011;2010:249842.

13. Riccio P. The molecular basis of nutritional intervention in multiple sclerosis: A narrative review. Complement Ther Med 2011;19:228–237.
14. Slawta JN, Wilcox AR, McCubbin JA, et al. Health behaviors, body composition, and coronary heart disease risk in women with multiple sclerosis. Arch Phys Med Rehabil 2003;84:1823–1830.
15. Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: Update on dietary requirements for brain. Part 1: micronutrients. J Nutr Health Aging 2006;10:377–385.
16. Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: Update on dietary requirements for brain. Part 2: macronutrients. J Nutr Health Aging 2006;10:386–399.
17. Swank RL. Multiple sclerosis: Twenty years on low fat diet. Arch Neurol 1970;23:460–474.
18. Swank RL, Goodwin J. Review of MS patient survival on a Swank low saturated fat diet. Nutrition 2003;19:161–162.
19. Reese D, Shivapour ET, Wahls TL, et al. Neuromuscular electrical stimulation and dietary interventions to reduce oxidative stress in a secondary progressive multiple sclerosis patient leads to marked gains in function: A case report. Cases J 2009;2:7601.
20. Wahls TL, Reese D, Kaplan D, Darling WG. Rehabilitation with neuromuscular electrical stimulation leads to functional gains in ambulation in patients with secondary progressive and primary progressive multiple sclerosis: A case series report. J Altern Complement Med 2010;16: 1343–1349.
21. wellness tf. Practical tips for mindfulness meditation. 2010. Online document at: http://www.timeforwellness.org/blog-view/practical-tips-for-mindfulness-meditation-103 Accessed July 29, 2013.
22. Miller WR, Rollnick S. Motivational Interviewing—Helping People Change. 3rd ed. New York: The Guilford Press, 2013.
23. Molenberghs G, Kenward MG. The direct likelihood method. In: Missing Data in Clinical Studies. John Wiley & Sons, Ltd., 2007:75–92.
24. Hsu JC. The factor analytic approach to simultaneous inference in the general linear model. J Computat Graph Statist 1992;1:151–168.
25. Ennis M, Thain J, Boggild M, et al. A randomized controlled trial of a health promotion education programme for people with multiple sclerosis. Clin Rehabil 2006;20: 783–792.
26. Hadgkiss EJ, Jelinek GA, Weiland TJ, et al. Health-related quality of life outcomes at 1 and 5 years after a residential retreat promoting lifestyle modification for people with multiple sclerosis. Neurol Sci 2013;34:187–195.
27. Lee D, Newell R, Ziegler L, Topping A. Treatment of fatigue in multiple sclerosis: A systematic review of the literature. Int J Nurs Pract 2008;14:81–93.
28. Andreasen AK, Stenager E, Dalgas U. The effect of exercise therapy on fatigue in multiple sclerosis. Multiple Sclerosis 2011;17:1041–1054.
29. Tomassini V, Pozzilli C, Onesti E, et al. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: Results of a pilot, randomised, double-blind, crossover trial. J Neurol Sci 2004;218:103–108.
30. Shinto L, Calabrese C, Morris C, et al. A randomized pilot study of naturopathic medicine in multiple sclerosis. J Altern Complement Med 2008;14:489–496.
31. Andersen O, Elovaara I, Farkkila M, et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 2004;75:706–710.
32. Mantia LL, Vacchi L, Rovaris M, et al. Interferon beta for secondary progressive multiple sclerosis: A systematic review. J Neurol Neurosurg Psychiatry 2013;84: 420–426.
33. Beiske AG, Naess H, Aarseth JH, et al. Health-related quality of life in secondary progressive multiple sclerosis. Multiple Sclerosis 2007;13:386–392.

Address correspondence to:
Terry L. Wahls, MD
Department of Internal Medicine
Veterans Administration Medical Center
601 Highway 6 West
Iowa City, IA 52246

E-mail: terry.wahls@va.gov