Spring 2010

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Abstract

Multiple sclerosis (MS) is an incurable neurodegenerative disease whose symptoms are only partially relieved by pharmaceutical intervention. Disability due to this disease process can impede activities of daily living and decrease quality of life, both for MS patients and for their care partners and families. A nonrandomized, nonblinded prospective cohort study of 45 patients with MS was undertaken to investigate the impact of an exercise program emphasizing resistance training on balance and gait. This article presents data for the first 33 participants to complete the study protocol. The exercise program consisted of twice-weekly 50-minute sessions for 6 months. At 3 months and 6 months, statistically significant improvements ($P < .05$) from baseline were observed for the following measures: Nine-Hole Peg Test, 2- and 3-second Paced Auditory Serial Addition Test, Modified Fatigue Impact Scale, NeuroCom Balance Master (NeuroCom International, Inc, Clackamas, OR), Timed Up and Go test, and Berg Balance Scale. Three-dimensional biomechanical gait analysis showed increased knee power generation during midstance and increased hip power generation during terminal stance. To determine whether individuals with varying levels of disability responded to exercise in a similar fashion, participants were divided into two subgroups based on Expanded Disability Status Scale score: little or no disability (EDSS score 1.0-4.0) and mild-to-moderate disability (EDSS score 4.5-6.5). No statistically significant differences in results were found. The results of this study indicate that participation in a resistance training program improves MS patients' ability to walk and to generate muscular forces during locomotion.

Introduction

Multiple sclerosis (MS) is the most prevalent progressive neurodegenerative disease among young adults.[1] It is characterized by altered conduction in the motor and sensory nerve pathways resulting from an autoimmune attack on components of the central nervous system (CNS). Axons, myelin, or myelin-producing cells, the oligodendrocytes, are the primary targets of the attack, with the resulting destruction or damage causing miscommunication between the commands given by the brain and muscle activation. The disease shows highly variable patterns of evolution and rates of disability accumulation.[2] In the past 15 years, various treatment methods have emerged that can slow disease progression, but a cure remains elusive. Although drug therapy can reduce the number and severity of relapses, patients generally continue to experience fatigue, muscle weakness, and balance problems. The disability resulting from this disease process can impede daily functioning and decrease quality of life, both for MS patients and for their care partners and families. There is fairly strong and consistent evidence that individuals with MS are less physically active than those unaffected by the disease, which is alarming given the high rate of inactivity among the general population.[3] Various causative factors are involved in inactivity in both people with MS and the general population.[4] The impact of inactivity may be greater in the MS population, because its health consequences are paired with the results of disease progression itself, including decreased social interaction and compromised mental health status.[3]

Exercise training programs have traditionally been discouraged in the MS population because of the belief that they might exacerbate fatigue and other MS symptoms. To the contrary, recent studies have demonstrated positive effects of physical therapy and increased physical activity in reducing pain and improving mobility in MS patients.[3,5] Structured exercise interventions have been shown to improve fitness and quality of life in people with MS.[6] As is the case in many chronic illnesses, patient access to physical therapy and exercise programs is often limited by insurance restrictions or inability to afford gym memberships or therapy services. In addition, little encouragement is given by health-care providers to participate in structured programs designed to improve or maintain strength and mobility.[4] Moreover, exercise programs and public fitness facilities are typically not very accommodating of people with disabilities, and appropriate programs may be unavailable, especially in rural areas.

Although exercise is gaining favor as a therapeutic strategy to minimize the loss of functional capacity in people with chronic diseases, it remains underutilized as an intervention strategy in the MS population. Moreover, health-care providers disagree on what type of exercise intervention would be most beneficial for people with MS. ln a review of exercise research in MS, White and Dressendorfer[7] reported that all studies of training programs showed positive outcomes that outweighed the potential adverse effects. White et al.[6] documented improvement in fatigue as measured by the Modified Fatigue Impact Scale (MFIS), disability as measured by the Expanded Disability Status Scale (EDSS}, exercise quantity or duration, walking speed, and strength following an 8-week progressive resistance training intervention. Despite the often unpredictable clinical course of MS, exercise programs designed to increase cardiopulmonary fitness, muscle strength, and mobility may also Facilitate activities of daily living and improve quality of life while reducing the risk of secondary disorders.

In a previous study by Filipi et al.,[8] 67 individuals with MS with varying degrees of disability displayed similar improvement of muscle strength after a 6-monrh program of twice-weekly resistance training. This activity level was well tolerated by even the most frail study participants, including individuals with EDSS scores of greater than 8.0. Strength improvement was corroborated by DeBolt and McCubbin,[9] who explored the use of home-based resistance training in 36 adults with MS. They found trends of improvement in gait and balance, although the results did not reach statistical significance.

Various studies have found resistance training to be associated with improved ambulation and decreased fatigue in MS patients.[9-11] Generally, however, these studies have been small (n = 8-12), and the exercise programs have been short (8-12 weeks) . In addition, full biomechanical gait evaluations to objectively gauge the extent of changes were not performed. Finally, these studies did not address balance deficits, a common impairment for individuals with MS.

The present study began with the following hypothesis: Standardized, structured resistance and balance training will improve gait, as well as balance and fatigue, in MS patients regardless of their level of disability. The purpose of the study was to quantify changes in gait and balance using full biomechanical evaluation following a 6-month intervention targeting balance and gait in 45 patients with differing levels of disability. Because of the robust initial results and the length of time needed to complete the full study, preliminary findings are reported here. Data were analyzed for the first 33 participants to complete the exercise intervention, who were categorized into two groups: little or no disability (EDSS score 1.0-4.0) and mild-co-mode rate disability (EDSS score 4.5-6.5).

Methods

Participants

The first 33 participants to enroll in this study and complete the study protocol are reported on here. These participants ranged in age from 24 to 54 years (mean ± SD age, 38.8 ± 10.7 years}; there were 11 male and 22 female subjects. This male-to-female ratio is representative of the sex distribution of MS, which affects females twice as often as males. Thirty-one patients were white, and two were black. The proportion of MS patients who are members of minority groups differs among regions, with regional variance of approximately 20%.

Participants were recruited from the general MS population by provider referral or direct advertisement. They were divided into two subgroups based on EDSS score: those with little or no disability (EDSS score 1.0- 4.0) and those with mild-to-moderate disability (EDSS score 4.5-6.5). All subjects were ambulatory, either independently or with the aid of a cane. Evaluations were performed at baseline, 3 months, and 6 months. Natural history studies have shown that, left untreated, MS results in physical decline, although the speed and degree of decline cannot be predicted. Because of this heterogeneity and the subsequent difficulty of obtaining matched controls, a "before and after" study design was used, with each individual acting as his or her own base-line control.

To be eligible for inclusion in the study, participants had to have received a laboratory-supported diagnosis of relapsing-remitting, secondary progressive, or primary progressive MS. In addition, they had to meet the following criteria: 1) competence to give informed consent, 2) age between 19 and 65 years, 3) ability to walk 25 feet with or without a cane or bracing, and 4) ability to verbalize a willingness to comply with the study's evaluation schedule. This included participation in an average of two sessions per week of standardized structured resistance training and three balance evaluations, one at each time point (baseline, 3 months, and 6 months). Finally, evidence was needed char participation in the study would not put the patient's health at undue risk.

The exclusion criteria were as follows: 1) inability to provide informed consent, 2) EDSS score of 7 or higher, inability to walk 25 feet with the use of an assistive device, 4) pregnancy, breastfeeding, or having given birth within 3 months of initiation of the study, and 5) diagnosis of any other neurologic disorder or disability chat would affect balance and mobility.

Evaluation Instruments

The evaluation instruments used in the study were the Modified Fatigue Impact Scale (MFIS), the Modified Fall Efficacy Scale (MFES), the Berg Balance Scale (BBS), the Timed Up and Go (TUG) test, the Multiple Sclerosis Functional Composite (MSFC), the NeuroCom Balance Master, and a three-dimensional (3D) gait-analysis system incorporating eight cameras and a Kistler force platform.

Modified Fatigue Impact Scale (MFIS)

The MFIS is a 21-item self-reported questionnaire on physical, cognitive, and psychosocial functioning. Easy to administer, it focuses on the ways in which MS-related fatigue affects everyday life. This instrument has been shown to have high face validity and sensitivity in discriminating the effects of MS-related fatigue from chose of fatigue stemming from other condirions.[12]

Modified Fall Efficacy Scale (MFES)

The MFES is a self-reported questionnaire designed to measure the fear of falling in 14 activities. It has high internal consistency and test-retest reliability and is a valid measure of falls self-efficacy in individuals with balance disturbance or falls.[13]

Berg Balance Scale (BBS)

The BBS consists of 14 functional subtests administered by a physical therapist. The BBS's specificity is strong, with high inter-rater and intrarater reliability and concurrent discriminant and predictive validity.[14]

Timed Up and Go (TUG) Test

The TUG rest measures the time in seconds needed by the individual to stand up from a chair, walk 3 m straight ahead, turn back and return to the chair, and sit down again. It has been found to be highly correlated with functional markers such as climbing stairs, balance, and gait speed and predictive of institutionalization, falls, and mortality.[15]

Multiple Sclerosis Functional Composite (MSFC)

The MSFC is a multidimensional composite measure with three components: the Timed 25-Foot Walk (T25FW), the Paced Auditory Serial Addition Test (PASAT), and a timed Nine-Hole Peg Test (NHPT) performed with each hand. It has been found to better reflect the identifying components of disability than the EDSS but remains difficult to integrate into routine clinical care.[16] The MSFC measures dimensions of the disease relevant to daily functioning and seems to be more sensitive to change over time change the EDSS.[17]

Balance Master

The Balance Master (NeuroCom International, Inc, Clackamas, OR) is the standard clinical cool for balance evaluation. It has been found to have highly reliable measures for sway (intraclass correlation coefficient [ICC] >0.90) and moderately reliable measures for movement time and path sway (ICC 0.78 and 0.83, respectively).[18] Its sensitivity for subjects with balance disorders is 95%.

Gait-Analysis System

A 3D gait-analysis system with eight cameras and a Kistler force platform was used. Primary analysis of gait mechanics included measures of joint kinematics and kinetics. Joint kinematics included relative joint angles during gait, while kinematics included ground reaction forces. Also measured were joint moments and powers, which provide information on the amount of force and type of muscle contraction of the muscle groups of the legs during walking. Kinematic and kinetic data were captured while participants walked at a self-selected pace over ground for a few strides. This protocol was repeated until sufficient data were available to analyze five complete, uninterrupted steps for each leg.

Statistical Analysis

Data analysis was performed using paired *t* tests and mixed-model analysis. Mixed-model analysis was used because of the numerous data point being compared. The level of statistical significance was set at $P < .05$.

Exercise Intervention

The resistance exercise program designed for this study consisted of twice-weekly exercise sessions lasting 50 minutes each for a total of 6 months. Participants were required to attend the exercise program for the full 6 months. Starting resistance or weight was determined by each individual's ability to perform 10 repetitions of the designated exercise within 30 seconds using correct form. Progression in weight or resistance was implemented when the final repetition of a 10-repetition set could be done with the same effort as the first. Weight or resistance remained constant if the participant's form was poor or increasing exertion was needed to complete the set. The format used was a 30-second exercise followed by a 30-second rest. Two to three sets of each exercise were performed before the participant moved on to the next exercise station.

Each exercise session included 5 to I0 minutes of warm-up stretching, 30 minutes of the resistance training exercises, and 5 to 10 minutes of cool-down stretching. The overall resistance training program had three phases (Table 1). Each exercise session focused on a single phase, and participants rotated through the phases to ensure equal participation in each phase. The first phase focused purely on strength improvement using stationary machines. Each machine exercised different areas, including the abdominals and legs. All machines were handicapped-accessible. During the second phase, the time was divided between the stationary machines and exercises to improve balance and dexterity. Balance exercises were conducted in a squat rack containing hand holds to provide stability and security and prevent falls. A combination of dumbbells, Swiss balls, and balance boards were used to improve conditioning, agility, and strength. Trainers provided one-on-one assistance as needed. The third phase focused on movements using free weights. A foot/ankle wrap was used to secure the weights for individuals with extremity weakness to protect them from weight-falling injuries. Extremities were exercised separately and unilaterally to allow both hands to be used for weight stabilization if needed and to provide adequate training for weakened extremities. Activities were completed using weight benches to maximize balance and coordination. Each phase of the program was designed to address balance and muscle strength, issues of special concern to MS patients, rather than overall conditioning.

Results

The exercise intervention program was found to be safe and well tolerated by the initial 33 participants in this study. No injuries or disease exacerbations were noted throughout the intervention period. Some participants experienced transient increased dizziness during exercises requiring them to lie flat. These exercises were modified to allow participants to perform them using inclined benches, and patients were provided with assistance when moving from station to station to ensure safety. No statistically significant differences in results were found between the two groups with differing disability levels.

Balance and Cognition

All parameters of the MSFC demonstrated clinical improvement after the 6-month exercise program, although results for walking speed did not reach statistical significance. Changes in PASAT performance indicated improved concentration and memory. The M.FIS result showed a decrease in fatigue. Improvements were noted in stride length and also were significant for physical improvement from daily ambulation with supervision or support to independent ambulation on level surfaces, per established biomechanical gait testing parameters.[19] Balance was also improved, resulting in a decrease in the fear of falling as measured by the MFES (Table 2).

Gait

Ground reaction force testing demonstrated increased movement of the center of mass in all three directions after training. Increased values for peak vertical loading, peak vertical unloading, and vertical loading rate indicated more vertical fluctuation of the center of mass during stance. Increased braking force and propulsive force showed increased anteroposterior movement during forward progression while walking. Increased range of motion at the hip after training indicates increased joint motion due to greater muscle activity. Evaluation of joint moments indicated increased torque (moment) at the hip and knee, allowing for better joint rotation and better support of the body as it moves over the foot during stance. Overall, changes at the knee and the hip for both joint moments and joint powers demonstrated a significant increase in the strength of the knee extensors and hip extensors. This increase in strength resulted in increased knee extensor moment, hip extensor moment, knee power generation during midstance, and hip power generation during terminal stance (Table 3).

Discussion

Despite the large quantity of evidence indicating the health benefits of regular physical activity or exercise, less than half of all adults obtain the recommended amount.[19] The Centers for Disease Control and Prevention has reported that 37.7% of US adults get insufficient amounts of physical activity or exercise and 13.5% are nor active at all.[20] This deficit is compounded by the addition of a chronic illness, such as MS.[3] Physical activity and exercise lower the risk of developing various diseases, including obesity, diabetes, cardiovascular disease, stroke, hypertension, and many cancers, as well as improving the symptoms of these diseases. Regular physical activity also promotes bone and muscle strength and decreases feelings of depression and anxiety.[20]

Table 1. **Exercise program used in the study**

Exercise	Primary muscles	Secondary muscles	Unilateral movement	Alternative movement
Phase I: Strength development				
Leg curl	Hamstrings	Hip flexors	y	Balance movement
Seated lat pulldown	Lats		y	NA
Back row	Overall back		y	NA
Seated leg extension	Quadriceps	Hip flexors	y	NA
Shoulder press	Overall shoulders		y	Dumbbell raise
Chest press	Overall chest	Shoulders	y	Dumbbell press
Abdominal crunch	Overall abdominals	Lower back	n	NA
Back extension	Lower back	Hip flexors	n	NA
Tricep extension	Triceps		y	NA
Bicep curl	Biceps		y	NA
Phase II: Balance, strength development				
Cable triceps extension	Triceps	Lower abdominals	n	Seated tricep extension
Rotator activity	Rotator muscles		y	NA
Pushup movement	Chest	Shoulders	n	Chest press
Swiss ball crunch	Overall abdominals	Hip flexors	n	Abdominal crunch
Supermen	Lower back	Hip flexors	n	NA
Calf raise/stretch	Ankles	Main calf muscles	y	NA
Balance movement	Overall body		n	NA
Swiss ball squat	Quadriceps	Hamstrings	n	NA
Dumbbell bicep curl	Biceps		y	NA
Phase III: Balance, unilateral focus, strength development				
Dumbbell chest press	Chest	Shoulders	y	NA
Dumbbell shoulder raise	Deltoids	Core	y	NA
Wrist roll	Hand strength	Finger dexterity	y	NA
Dumbbell bicep curl	Biceps	Core	y	NA
Lat pushdowns	Overall back	Core	y	Lat pulldowns
Elbow bridges	Overall core	Hip flexors	n	Back extensions
Calf raise/stretch	Ankles	Main calf muscles	y	NA
Balance movement	Overall body		n	NA
Step movement	Hip flexors	Cardio	y	NA

Abbreviation: NA, not applicable.

According to the US Department of Health and Human Services' report *Healthy People 2010*, more than half of people with a chronic disease such as MS do not participate in any leisure-time physical activity or exercise,[21] despite its benefits in the treatment and prevention of chronic disease.[22] The severity and frequency of MS symptoms may impede participation in exercise programs, leading to physical inactivity that often increases the risk of other diseases related to a sedentary lifestyle.[6,23] Excessive fatigue, poor balance, and motor weakness may have detrimental effects on overall physical functioning by limiting body movement. Moreover, MS patients' sensitivity to heat can limit when and where activity can be performed.[1] Motl and colleagues[24] reported that the number of MS symptoms experienced by an individual within the preceding 30 days was inversely related to his or her amount of physical activity. Physical inactivity becomes even more worrisome if, as in stroke treatment, there is a "window of opportunity'' 7 to 14 days after acute injury for maximum rehabilitation of the CNS.

Table 2. Mean scores for the MSFC, MFIS, and MFES at baseline, 13 weeks, and 26 weeks

Test	Baseline	13 weeks	26 weeks	P value[a]
MSFC				
NHPT, right, s	27.154	24.669	24.316	.003
NHPT, left, s	26.736	25.818	25.110	.009
PASAT, 3 s, No. of correct answers	68.733	74.667	78.722	.002
PASAT, 2 s, No. of correct answers	52.322	58.411	62.333	.000
T25FW, s	6.865	6.752	6.618	.394
MFIS, Physical	22.856	16.900	17.333	.000
MFES	8.27	8.89	8.79	.0457

Abbreviations: MFES, Modified Fall Efficacy Scale; MFIS, Modified Fatigue Impact Scale; MSFC, Multiple Sclerosis Functional Composite; NHPT, Nine-Hole Peg Test; PASAT, Paced Auditory Serial Addition Test; T25FW, Timed 25-Foot Walk.

[a]Baseline versus 26 weeks.

Physical activity and exercise improve strength in people with MS, increasing muscle tone and improving oxidative capacity. Whether exercise can produce changes in CNS functioning (ie, neuroplasticity) remains unknown, although Daly and Ruff[25] described motor-learning principles required for the development of effective motor-recovery interventions for stroke patients based on evidence of brain plasticity. Little information is available about needed motor-learning principles and resistance training in patients with MS[26] or other CNS problems, with the majority of studies based on aerobic activities such as ergometry, treadmill exercise, or swimming. Regardless, it has been demonstrated that individuals who stay active remain independent longer, with slower disease progression. This may indicate anti-inflammatory properties of physical activity, improvement of neuronal pathways, rechanneling and retraining of conduction pathways, or simply a basic response of healthier tissue.

The preliminary results of this study suggest that resistance training reduces fatigue, a finding consistent with previous research.[27] It is not known whether this improvement in fatigue is due to increased efficiency of movement, decreased levels of inflammatory cytokines, release of endorphins, or psychological factors.

Resistance training in patients with MS, along with balance and gait training, must be performed in a safe environment and be supervised by adequately trained staff. A slow increase in resistance that is matched to the endurance level of the patient will result in gradual improvement in strength, balance, and walking ability. On the other hand, aggressive training is not well tolerated and can result in injury, severe fatigue, and disease exacerbations. Unilateral training is recommended, with decreased resistance and workload for weakened limbs to encourage muscle movement and toning. Increases in resistance should be implemented only when the individual can perform 10 repetitions with appropriate form. It has been reported that 40% of MS patients experience symptom exacerbation during and immediately after exercise because of a rise in core temperature.[28] Resistance training, however, does not increase core temperature to the extent seen in endurance training and thus may be better tolerated by people with MS. In the present study, no injury, long-term ill effect, or disease exacerbation was noted. The exercise intervention was well tolerated by all participants, regardless of level of disability. Further research is warranted to determine

whether these results are reproducible.
These data are from a small sample, making it difficult to generalize the results to a broader population. In addition, the study was nonblinded and nonrandomized. However, evaluations and data collection were performed by independent examiners rather than by the primary investigator in order to avoid bias. It is anticipated that the complete study data will support the preliminary findings, particularly in light of the robust nature of the initial results.

***Table 3.* Comparison of mean gait-evaluation measures between baseline and 6 months**

Gait evaluation measure	Result	*P* value
Ground reaction forces		
Vertical active loading peak (weight transfer at heel strike)	Increased	.018
Vertical active unloading peak (weight transfer at toe-off)	Increased	.017
Loading rate	Increased	.0006
Braking force (FyB)	Increased	.003
Propulsive force (FyP)	Increased	.025
Ratio of braking force to propulsive force (FyB:FyP)	Increased	.002
Propulsive impulse	Increased	.038
Stance time	Decreased	.025
Joint angles		
Hip range of motion	Increased	.013
Joint moments		
Peak knee extensor at midstance/ late stance	Increased	.010
Peak hip extensor at early stance/ heel strike	Increased	.003
Peak hip extensor at late stance	Increased	.035
Joint powers		
Knee eccentric contraction of extensors: power absorption at K3, late stance	Increased	.001
Hip concentric contraction of extensors: power generation at terminal stance	Increased	.006

Conclusion

As is the case for the general population, exercise significantly improves the overall condition of people with MS. Participation in a structured resistance training program has positive effects on gait, balance, and level of fatigue, as well as cognition. Thus exercise, particularly a structured weight resistance program, should be considered an essential component of comprehensive MS care, to be used in combination with pharmaceutical intervention and physical therapy.

Acknowledgments

All authors made significant contributions to the content of the original and revised versions of the manuscript. We acknowledge Sangeeta Agerwal, MS, for statistical support and Lauro Bilek, PhD, PT, for editorial assistance. We are also grateful to Claire Haire, MSN, Study Coordinator, and the other members of the University of Nebraska Medical Center/Nebraska Medical Center (UNMC/NMC) Clinical Research Center for their organizational assistance and support, as well as to Jennifer McKune, PT, for patient evaluation assistance and Kathi Healy for assistance with patient recruitment. This project was funded by the MARS Foundation of Ames, IA, the National Multiple Sclerosis Society, and the UNMC/NMC Clinical Research Center.

Financial Disclosures

Dr. Filipi has served as a paid consultant for Biogen Idec, Berlex, EMD Serono, and Teva Neuroscience. She currently receives research funding from Proctor & Gamble/Aventis Pharmaceuticals. Dr. Leuschen currently receives research funding from Proctor & Gamble/Aventis Pharmaceuticals. Ms. Huisingo currently receives American Society of Biomechanics Grant-In-Aid funding for doctoral research. Dr. Stergiou currently receives research funding from the National Institutes of Health (K25HD047194), the National Institute on Disability and Rehabilitation Research (H133G040118), and the Nebraska Research Initiative. Ms. Schmaderer, Ms. Vogel, and Mr. Kucera have no conflicts of interest to disclose.

Practice Points

- Disability due to MS can impede activities of daily living and decrease quality of life, both for MS patients and for their care partners and families.

- The addition of a structured exercise program to the treatment regimen of MS patients can result in significant improvement in overall physical condition. Participation in a structured weight resistance program is associated with improvements in gait, balance, and level of fatigue as well as cognition.

- A comprehensive management strategy for individuals with MS should include exercise in combination with pharmaceutical intervention and physical therapy.

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