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ORIGINAL ARTICLE

Constraint-Induced Movement Therapy for the Lower Extremities in Multiple Sclerosis: Case Series With 4-Year Follow-Up

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Abstract

Objective: To evaluate in a preliminary manner the feasibility, safety, and efficacy of Constraint-Induced Movement therapy (CIMT) of persons with impaired lower extremity use from multiple sclerosis (MS).

Design: Clinical trial with periodic follow-up for up to 4 years.

Setting: University-based rehabilitation research laboratory.

Participants: A referred sample of ambulatory adults with chronic MS (N=4) with at least moderate loss of lower extremity use (average item score ≤6.5/10 on the functional performance measure of the Lower Extremity Motor Activity Log [LE-MAL]).

Interventions: CIMT was administered for 52.5 hours over 3 consecutive weeks (15 consecutive weekdays) to each patient.

Main Outcome Measures: The primary outcome was the LE-MAL score at posttreatment. Secondary outcomes were posttreatment scores on laboratory assessments of maximal lower extremity movement ability.

Results: All the patients improved substantially at posttreatment on the LE-MAL, with smaller improvements on the laboratory motor measures. Scores on the LE-MAL continued to improve for 6 months afterward. By 1 year, patients remained on average at posttreatment levels. At 4 years, half of the patients remained above pretreatment levels. There were no adverse events, and fatigue ratings were not significantly changed by the end of treatment.

Conclusions: This initial trial of lower extremity CIMT for MS indicates that the treatment can be safely administered, is well tolerated, and produces substantially improved real-world lower extremity use for as long as 4 years afterward. Further trials are needed to determine the consistency of these findings.

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Impaired mobility is a major cause of reduced quality of life in patients with multiple sclerosis (MS).[1,2] Accordingly, over the past 30 years, nearly 100 peer-reviewed studies have investigated various forms of physical therapy involving the lower extremities for MS, including standard inpatient rehabilitation[3] and experimental outpatient approaches such as aerobic exercise,[4] progressive resistance strength training,[5] and robotic therapy.[6] Although such physical training can improve or maintain physical endurance, limb strength, cardiopulmonary fitness, or general well-being,[4,7-9] for the most part the studies to date have not evaluated whether the training benefits can transfer from the clinic or laboratory—where measurement is made primarily of maximal performance after prompting by the experimenter—to *spontaneous* use of the impaired limbs in the real world after return to the community.

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An additional important consideration is that experimental physical rehabilitation approaches to MS to date have only seldom used the type of methods to increase the relevance of therapies for activities in the life situation, of the sort used in various behavioral analysis programs for the control of obesity, smoking, or alcohol abuse.[10-12] Indeed, such approaches are not formally or systematically incorporated in physical rehabilitation for neurologic disorders in general. Nonetheless, a few recent studies have suggested that these techniques can bolster outcomes from physical rehabilitation. Studies on low back pain have shown that combining several techniques that are designed to increase the patients' adherence to the treatment (a treatment contract, emphasizing to patients their active participation in the treatment outcome, and maintaining a home diary) with exercise training can significantly improve self-rated disability over several years of follow-up relative to the same exercise training without such techniques.[13,14] More recent research has shown that upper extremity Constraint-Induced Movement therapy (CIMT) for poststroke hemiparesis that includes procedures to increase the relevance for everyday life of the training for the patient (see the Intervention section) can produce significant improvements in real-world upper extremity use, as assessed by the Motor Activity Log (MAL),[15] compared with task-oriented training without these procedures.[16] Moreover, this study showed that CIMT was associated with significant cortical gray matter increases over sensorimotor areas (as determined by voxel-based morphometry of brain magnetic resonance imaging scans), while there was no gray matter change after task-oriented training alone.

Numerous studies have shown that CIMT can successfully treat the reduction of spontaneous upper extremity use in the real world after stroke,[15-18] MS,[19] traumatic brain injury,[20] and cerebral palsy.[21] Moreover, specially adapted forms of CIMT have also successfully treated real-world lower extremity deficits after stroke[22-24] and spinal cord injury,[25] as well as verbal communication deficits in poststroke aphasia.[26-28] Regardless of the part of the body that is primarily affected, the goal of CIMT is to overcome either the reduced spontaneous use or the maladaptive use of the more-affected part of the body during functional activities. The term *Constraint-Induced Movement therapy* is considered appropriate to designate the upper extremity form of the treatment as well as the variation for the lower extremities, since the term *constraint* is meant to refer to either physical restraint of a less impaired extremity by a device or constraints imposed by behavioral procedures that limit use of compensatory strategies, or both.

Because of (1) the almost complete absence in MS rehabilitation research to date either of treatment techniques that are explicitly designed to transfer therapeutic gains achieved in the clinic to the real world or of the measurement of real-world functional outcomes, (2) the previously demonstrated success of upper extremity CIMT for chronic progressive MS,[19] and (3) the strong imposition that impaired mobility has on the quality of life in MS, we undertook a pilot trial of lower extremity CIMT for persons with chronic MS who had impaired mobility but were still capable of walking. We hypothesized that, similar to the patients with MS who had undergone experimental upper extremity CIMT, persons with relatively stable chronic MS and impaired mobility would demonstrate large treatment effects in real-world mobility and maintain their improvement long after the end of treatment. In addition, in accordance with prior studies in stroke rehabilitation, including CIMT,[15-18,29] we anticipated that changes in neurologic impairment might not parallel changes in real-world disability. We report here the immediate posttreatment results as well as follow-up results over 4 years.

List of abbreviations:

CIMT	**Constraint-Induced Movement therapy**
d'	**effect size**
EDSS	**Expanded Disability Status Scale**
FP	**functional performance**
LE-MAL	**Lower Extremity Motor Activity Log**
LE-MFT	**Lower Extremity Motor Function Test**
MS	**multiple sclerosis**
6MWT	**6-minute walk test**
T25W	**timed 25-foot walk test**
VAS	**visual analog scale**

Methods

Participants

Four ambulatory adults with chronic MS and moderately severe mobility impairments were recruited from our institution's MS clinic. Inclusion criteria included MS diagnosed according to the revised McDonald criteria,[30] no disease relapse for at least 3 months, gait impairment attributable only to MS based on the clinical impression of a specialty MS neurologist (K.B.), no more than mild pain in the lower extremities, absence of medical conditions that would preclude intensive lower extremity training (eg, foot ulcers, advanced arthritis), ability to walk at least 16m 5 times a day with or without an assistive device but without the aid of another person, score $\geq$24 on the Mini-Mental State Examination, and score $\leq$6.5/10 on the functional performance (FP) subscale of the Lower Extremity Motor Activity Log (LE-MAL, see the Outcomes section). The clinical and demographic features of the participants are provided in table 1. Progressive forms of MS (either primary progressive or secondary progressive disease) had been diagnosed in 3 of the patients. These patients had Expanded Disability Status Scale (EDSS)[31] scores of 6.5 to 7.0 (maximum possible, 10.0), indicating the need for constant bilateral assistance from devices to walk short distances without resting. Although the fourth patient had received a diagnosis of relapsing-remitting disease, she could not recall having had any disease relapses. She had a milder EDSS score of 4.0, indicating that she could walk without assistance at least 500m, but nonetheless required an ankle-foot orthosis for right lower extremity stabilization because of mild hemiparesis.

Intervention

Regardless of the specific adaptations used, the core features of CIMT are (1) massed practice with the impaired part of the body on functionally relevant tasks, (2) discouragement of compensatory activities, (3) shaping of behavior on training tasks to progressively improve performance in small steps, and (4) a set of procedures to transfer gains from the clinic to the real world.[32,33] The latter set of procedures, collectively termed the "transfer package," includes a behavioral contract to carry out agreed-on activities signed by the patient, therapist, and a witness, daily reporting by the patient of the extent of real-world use of the impaired function, problem solving to help overcome perceived barriers to improved performance, daily home practice exercises, and a home practice diary. In so doing, the transfer package is

Table 1 Characteristics of treatment sample

Patient No.	Age (y)	Sex	MS Subtype	Disease Chronicity (y)	EDSS Score (Maximum, 10.0)	Mean Initial Daily Fatigue VAS (Maximum, 100)*
1	62	M	PPMS	4.6	6.5	54.2
2	45	M	SPMS	17.0	6.5	60.0
3	60	F	PPMS	19.0	7.0	27.5
4	63	F	RRMS	14.1	4.0	9.3
Mean ± SD	57.5±8.4			13.7±6.4	6.0±1.4	37.8±23.7

Abbreviations: F, female; M, male; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.
* Participants' ratings began on the first treatment day except for patient 1, whose ratings began on the third treatment day.

designed to increase the real-world relevance of the physical therapy program for the participant.

Although upper extremity CIMT characteristically uses a physical restraint such as a padded mitt on the less-affected arm to support behavioral constraint, such a device is not used for lower extremity CIMT because both lower extremities must be simultaneously engaged for weight-bearing on massed practice tasks. Instead, discouraging compensatory maladaptive behaviors is accomplished, for example, by providing praise when stance time for the 2 lower extremities during ambulation is approximately equal, or as part of the transfer package, for example, by requiring home practice exercises for the lower extremities as opposed to being sedentary. For lower extremity CIMT, task practice includes partial body weight–supported treadmill training, overground ambulation, stair climbing, stepping over obstacles, and balance training (bending to pick up objects when standing, among other exercises).[22]

In our study, each patient was trained on lower extremity CIMT by an experienced staff physical therapist for 52.5 hours over 15 consecutive weekdays (ie, 3.5h/d for 3wk). Each treatment session consisted of 30 minutes for the transfer package components and 3 consecutive hours of task training using the behavioral technique termed *shaping*.[34] Each patient was trained on about 15 different tasks that were selected after mutual agreement with the therapist. Patients rated their level of physical fatigue on a visual analog scale (VAS) after each training exercise to allow monitoring for practice-related fatigue, and they were given rest periods as often as needed in the judgment of the therapist.

Outcomes

The primary outcome was the mean item posttreatment score on the FP subscale of the LE-MAL.[22,35] The LE-MAL is a scripted structured interview conducted by the therapist that asks patients to rate each of 14 common daily living activities that involve the lower extremities (the items comprising this test are listed in table 2) with an 11-point Likert-type scale that quantifies functional performance (0, cannot do; 10, completely normal). The participants were asked to rate the quality of their performance on the activities in the course of daily life over the week before assessment, daily during treatment, immediately after treatment, and at specified times in follow-up. Although the LE-MAL has not been validated for people with MS, it has excellent psychometric properties for those with stroke. Findings from chronic ambulatory patients with stroke (n=13)[36] indicate that the LE-MAL FP subscale has a test-retest correlation of .94 and is highly correlated with the Late Life Function and Disability Instrument[37] (r=.93, P<.01) and the Stroke Impact Scale (r=.87, P<.01).[38]

We also evaluated posttreatment change on several measures of maximum lower extremity movement ability after prompting in the laboratory. These measures were as follows:

1. *Lower Extremity Motor Function Test (LE-MFT).*[22,35] The LE-MFT (table 2) is a lower extremity analog of the Wolf Motor Function Test,[15] which is widely used to assess upper extremity movement ability. The LE-MFT contains items from the Berg Balance Scale test, the Duke Mobility Skills Profile (Functional Reach Test), and the Dynamic Gait Index. Fifteen of the 16 activities on the LE-MFT are required to be performed as fast as possible and are reported by their performance times.

Table 2 Individual test items from the LE-MAL and the LE-MFT

Item No.	LE-MAL	LE-MFT
1	Walking indoors	Sit to stand
2	Walking outdoors	Stand/forward reach*
3	Climbing stairs	Turn 360° to right
4	Stepping over object	Turn 360° to left
5	Turning around while standing	Place right foot on stool
6	Standing from chair	Place left foot on stool
7	Standing from toilet	Place right foot on stool with 5-lb (2.3-kg) weight
8	Entering/exiting bed	Place left foot on stool with 5-lb (2.3-kg) weight
9	Entering/exiting bath or shower	Standing/abduction slide to right
10	Entering/exiting car	Standing/abduction slide to left
11	Open a door with a doorknob while standing and walking through	Step over shoeboxes
12	Wash hands while standing at sink	Retrieve object from floor
13	Reaching into cabinets above shoulder level	Look over shoulder while walking
14	Retrieving object from floor from standing position	Gait and pivot turn to right
15		Gait and pivot turn to left
16		Ascend/descend 3 steps

* This activity is not timed but instead measured by the maximal distance that the subject can reach.

2. *Timed 25-foot walk test (T25W)*. The T25W is the most widely used gait assessment in MS. It is a measure of how much time is required to walk 25ft (approximately 8m) as fast as possible.[39]
3. *Six-minute walk test (6MWT)*. The 6MWT, which measures how far patients can maximally walk in 6 minutes, is highly correlated with subjective measures of ambulation and fatigue in MS.[40]

Both the T25W and the 6MWT are moderately to highly correlated with accelerometry-based step counts in the community among persons with stroke.[41]

After treatment, patients were followed up by telephone at 4 weeks, 6 months, 1 year, 2 years, and 4 years to determine their concurrent LE-MAL scores.

During the course of treatment, patients rated their overall fatigue at the end of training tasks using a 100-mm linear VAS.[42] We used the change in the mean daily fatigue VAS score between the beginning and end of the course of treatment as a third outcome measure.

Analysis

Because of the small size of our patient sample, the individual outcomes are described using a case report approach. When outcomes are characterized at a group level (see Discussion), descriptive statistics (mean, SD, effect size) rather than inferential statistics are used. Effect sizes are described using *d'*, which is appropriate for within-subjects designs. To calculate *d'*, the mean change in an outcome is divided by the SD of the change; by convention, *d'* values $\geq$.57 are considered large.[43]

Ethics committee approval

This study was approved by our university's Institutional Review Board for Human Use. All study participants provided informed consent.

Results

Table 3 indicates the changes at posttreatment from pretreatment for each individual patient on the LE-MAL, the various laboratory motor tests, and the fatigue scores, and table 4 indicates the longitudinal LE-MAL scores from our patients in relation to the time of their CIMT.

Table 3 Changes in spontaneous real-world lower extremity use (LE-MAL), maximal motor ability in the laboratory (LE-MFT, T25W, 6MWT), and fatigue (VAS) immediately after CIMT

Patient No.	LE-MAL	LE-MFT (s)	6MWT (m)	T25W (s)	VAS*
1	2.9	−9.6	20.4	−19.3	−0.9
2	1.3	−1.8	57.3	−8.1	−7.5
3	2.3	−0.3	NT	2.1	−10.8
4	2.5	0.0	39.0	−1.2	0.7
Mean ± SD	2.3±0.7	−2.8±4.7	38.9±18.6	−6.6±9.5	−4.6±5.4
d'	3.3	0.6	2.1	0.7	0.9

Abbreviation: NT, not tested.
* Final VAS ratings were obtained on the last treatment day (day 15) except for patient 4, from whom no further ratings were obtained after treatment day 13.

Case 1

The first patient was a 62-year-old owner of an insurance company with primary progressive MS for the preceding 6 years. His only other medical illnesses were hypercholesterolemia and hypertension. At the time of enrollment he was taking baclofen, modafinil, hydrochlorothiazide, atenolol, aspirin, escitalopram, and rosuvastatin. He had unilateral optic neuritis, bilaterally diminished sensation in his fingers, occasional spasms in his left leg, mild depression, subjective cognitive difficulties, urinary urgency and hesitancy, and irregular bowel movements. He had moderate paresis of his left leg and slightly increased tone in both legs. He used a walker or wheelchair for long distances or when tired, but could stand with bilateral assistance; his gait was unsteady. His EDSS score was 6.5.

Immediately after CIMT he gained 2.9 points on the LE-MAL FP scale, reduced his mean LE-MFT time by nearly 10 seconds, increased his 6MWT distance by 20m, and reduced his T25W test by 19 seconds (see table 3). His posttreatment fatigue rating negligibly declined by 0.9 points. Five months later, his neurologist noted that the patient had changed from relying on a walker to a cane for household ambulation, had improved endurance, and had less depression. When reassessed by his neurologist 1 year later, he noted gradual worsening in his walking ability, increased wheelchair reliance, and increased fatigue. Nonetheless, his LE-MAL score had increased remarkably over the preceding year, having improved at this time by 1.9 points beyond his posttreatment score. Unfortunately, at 22 months after CIMT, he was found to have an unrelated illness that proved to be fatal before he could undergo his 2-year follow-up with us.

Summary

The patient's considerable improvement on the LE-MAL after CIMT was initially paralleled by marked improvement of both his maximal movement ability on the LE-MFT and his neurologic symptoms. At the 1-year follow-up there was slight symptomatic worsening but still a considerably improved LE-MAL.

Case 2

The second patient was a 45-year-old engineer with MS diagnosed 17 years earlier. Although he was considered by his neurologist to have secondary progressive MS at the time of study entry, he could not recall ever having had a disease relapse, nor was such reported in his available medical records. His only other illness was hypertension. He had moderate weakness of his right leg, diminished somatic sensation, paresthesias, stiffness in his lower extremities, and bilateral Babinski signs. Other symptoms included urinary urgency, fatigue, and heat intolerance. He used a cane for walking short distances and a wheelchair for longer distances. His gait was broad-based and unsteady, and he was unable to perform tandem walking. He was managed with combination interferon beta-1b and mitoxantrone, baclofen, bisoprolol/hydrochlorothiazide, nortriptyline, and tolterodine. His EDSS score was 6.5.

His posttreatment improvement on the LE-MAL was 1.3 points, which was the least gain among our patients. In contrast, his performance time on the LE-MFT improved by nearly 2 seconds, his 6MWT distance improved by 57m (the most among our patients), and his T25W decreased by 8 seconds. Furthermore, his fatigue rating at the end of treatment had improved by nearly 8 points.

Table 4 LE-MAL FP scores for each case at each assessment point

	Time in Relation to Treatment						
Case No.	Pre	Post	4wk	6mo	1y	2y	4y
1	2.7±1.0	5.6±0.5	7.5±0.7	7.5±0.7	7.5±0.7	N/A	N/A
2	3.1±1.0	4.4±0.7	4.0±0.4	4.0±0.4	4.1±0.8	2.2±0.8	2.2±0.8
3	3.2±0.8	5.4±0.9	6.7±0.7	6.7±0.7	5.9±2.8	5.7±3.2	5.7±3.2
4	6.5±0.7	9.0±0.0	8.9±0.7	8.9±0.7	6.9±1.4	7.7±1.3	7.7±1.3

NOTE. Values are mean ± SD.
Abbreviation: N/A, not available.

At about 4 months posttreatment he noted worsening fatigue, followed a month later by slowing of his gait and diminished bimanual dexterity. At 1-year follow-up, his LE-MAL score had decreased slightly but was still well above his pretreatment score. By 14 months posttreatment he felt his legs had become weaker and that he had increased numbness and paresthesias, as well as reduced ability to maintain his balance and worse urinary urgency. At 22 months posttreatment a rapid worsening of his symptoms had prompted a brief hospitalization for treatment with intravenous methylprednisolone and inpatient physical therapy, but without symptomatic benefit. At this time and at subsequent neurologic evaluations his EDSS score fluctuated between 6.5 and 7.0. His LE-MAL score declined to 2.2, nearly a full point below his baseline value. He changed from using a cane to a walker. At 3 years posttreatment he noted increased spasms of his right leg as well as his left arm, and he became primarily reliant on a wheelchair for locomotion. At 4 years posttreatment he had acquired subjective heaviness of his arms, with LE-MAL scores unchanged from the 2-year assessment.

Summary
This patient showed the least gain in our series at posttreatment on his LE-MAL. He showed minimal improvement on the laboratory motor tests except the 6MWT, which was the greatest improvement among our patients. After the first year he declined in both his neurologic symptoms and his LE-MAL score, falling in the latter to below baseline by the 2-year follow-up and remaining at this level for the remaining 2 years.

Case 3

The third patient was a 60-year-old retired insurance agent who had primary progressive MS diagnosed 20 years earlier. She noted occasional spasms in her legs, and primarily used a walker for household locomotion and a wheelchair for longer distances. She also had bowel and bladder urgency, fatigue, heat intolerance, and tinnitus. She had moderate bilateral leg weakness and was unable to perform tandem walking. Her medical history was notable also for nonmetastatic breast cancer that had resolved with a lumpectomy, and bursitis of her right shoulder. At the time of CIMT she was taking celecoxib, amantadine, sertraline, atenolol, baclofen, tizanidine, venlafaxine, tolterodine, and letrozole. Her EDSS score was 7.0 immediately before CIMT.

Her posttreatment LE-MAL improved by 2.3 points, but she had scant changes on her LE-MFT and T25W. (The 6MWT had been inadvertently omitted.) She had a substantial reduction in her fatigue rating by 11 points. At 4 months after CIMT her EDSS score had improved to 6.5. At 1-year follow-up her average LE-MAL score had improved still further from its posttreatment level by 0.3 points. However, at this point she had also become unable to climb stairs or step over objects independently. Her complaints of increased lower extremity stiffness, weakness, and spasms, along with diminished sensation in her left fingers, prompted a brief hospitalization for treatment with intravenous methylprednisolone and oral prednisone, which was followed by a reduction of her spasms. At 16 months after CIMT her legs felt heavier. By 2 years after CIMT she had become unable to walk outdoors independently. Nonetheless, her LE-MAL score had changed only negligibly. It remained stable for the remainder of her follow-up, 2.4 points higher than baseline. At 28 months posttreatment she noted reduced motivation, emotional incontinence, depression, and anxiety. Her examination demonstrated bilateral lower extremity spasms with passive movement, and decreased vibratory sense in her toes. At $2^1/_2$ years posttreatment she felt that her left leg was weaker than her right leg, along with mild weakness of her fingers. A few months later she noted distal cold sensations in her extremities and a constant sensation of leg heaviness. She reported increased reliance on a wheelchair in the home. She began methylphenidate for increased fatigue, which she found beneficial. For the remainder of her follow-up course she noted gradual worsening of her lower extremity symptoms, but without further loss in her lower extremity function.

Summary
The patient had substantially improved on her LE-MAL and fatigue rating at posttreatment but showed negligible change in her laboratory motor tests. Shortly afterward her EDSS score also improved. Her LE-MAL score peaked at 6 months, declined slightly at 1 year, and then remained essentially unchanged for the remainder of follow-up. However, while she declined in a few of her individual lower extremity activities for the remainder of follow-up, the others were unaffected. Thus, even though there was a gradual and diffuse worsening in her MS symptoms for the last 2 years of follow-up, the improved function on specific functional tasks persisted.

Case 4

The fourth patient was a 63-year-old nurse who had relapsing-remitting MS diagnosed 14 years earlier but could not recall any disease relapses. She had mild right leg weakness with a foot drop, bilaterally increased tone in the legs, a right Babinski sign, and occasional nocturnal spasms in the leg. Her right arm was also mildly ataxic. Medical history was notable also for cervical spondylosis, arthritis, coronary artery disease, hypertension, hyperlipidemia, and an ovarian malignancy that had been surgically cured 12 years earlier. Medications included weekly interferon beta-1a,

isosorbide mononitrate, diltiazem, estrogen, aspirin, esomeprazole, imipramine, atorvastatin, and polyethylene glycol.

Immediately after CIMT her LE-MAL score had improved by 2.5 points and her 6MWT distance had gained 39m, but her LE-MFT, T25W, and fatigue ratings had shown essentially no changes. At 2 months posttreatment she reported to her neurologist that she felt markedly improved in her foot drop, ambulation, and balance. However, by 9 months posttreatment she noted more impaired gait and balance, with 3 falls over $1^1/_2$ months. She also noted progressive difficulty with handwriting, heaviness of her right arm, urinary urgency with frequency and incontinence, increased fatigue, and sadness without frank depression. The aggravated symptoms were judged by her neurologist to represent a relapse but were not treated. By this time her LE-MAL had lost most of its gains from her baseline. But 2 months later she felt considerably improved in her motor control. By her 2-year follow-up her LE-MAL score had rebounded with a net increase of 1.2 points above baseline, a gain that she maintained at least up to her 4-year follow-up. By $2^1/_2$ years after CIMT her gait speed had declined, and she noticed increased right leg weakness. She felt an increased need to hold on to objects when walking. Her EDSS score had worsened from 4.0 at the time of CIMT to 6.0. Her neurologist's impression was that the patient was advancing to the secondary progressive form of illness. For the remainder of her follow-up her illness was stable. At her neurologist's recommendation she began aquatic therapy twice a week after her 2-year follow-up with us and reported that her walking ability seemed improved after each pool therapy session.

Summary

Initially, this was the least impaired of our patients. Her posttreatment LE-MAL improvements over the first year paralleled those of case 3. At posttreatment she had a substantial improvement on her 6MWT, but not the other motor tests. Soon after treatment she noticed considerably improved and sustained lower extremity movement ability. At about 1 year posttreatment, however, her neurologic symptoms had markedly worsened, with a parallel drop in her LE-MAL score. For the remainder of follow-up, however, the LE-MAL returned close to her immediate posttreatment level, while again, paradoxically (similar to case 3), she developed progressive neurologic decline and a marked worsening of her EDSS score. In the final 2 years she found that twice-weekly pool exercises transiently benefited her walking ability.

Discussion

All 4 patients had gained substantially in their spontaneous lower extremity motor function in daily life from pre- to posttreatment (mean LE-MAL gain $\pm$ SD: 2.3$\pm$0.7 points, $d'=3.3$; see table 3). In addition, they showed no diminution in gains from posttreatment to their 1-year follow-up, with the exception of case 4, who may have had a short-term relapse but then subsequently rebounded and thus almost completely recovered from her setback (see table 4). For the 3 patients for whom 4-year follow-up was available, 2 still had considerably better real-world function than before treatment, while 1 had worse function than before (see table 4).

Three of the 4 patients, depending on the measure, had immediate posttreatment gains on the laboratory tests of lower extremity motor function (see table 3), for which movement was prompted rather than performed spontaneously. As a group, the patients had a very large posttreatment effect size on the 6MWT ($d'=2.1$), and smaller but still large effect sizes on the LE-MFT ($d'=0.6$) and the T25W ($d'=0.7$).

The neurologic courses of the patients were typical for persons with MS who are in the chronic phases of their illnesses, with diffuse and gradual worsening of their neurologic impairments.[44] Nonetheless, despite apparent neurologic progression, all of our patients had maintained their posttreatment improvement in lower extremity real-world function for at least 6 months. Patient 4 appeared to have had a brief relapse at 1 year that may have cost her most of her post-CIMT functional gains, but subsequently she had almost completely recovered her previous functional gains without additional CIMT. Altogether, these findings suggest that CIMT can promote sustained functional improvement in disabling MS that affects the lower extremities, even when patients confront progressive neurologic loss, and after just a single course of treatment. Dissociation between changes in neurologic impairment and disability after rehabilitation has been previously observed in stroke and MS,[15-19,29] which indicates that these categories of response are not tightly interrelated. Two of the patients maintained their functional improvements for as long as 4 years posttreatment, despite apparent clinical disease progression.

To our knowledge, no other physical therapy studies of MS have assessed the transfer of treatment gains to spontaneous lower extremity use in the real world or followed up patients for as long after a single course of treatment. Our findings also suggest that lower extremity CIMT for MS is safe and well tolerated when provided by experienced therapists. This outcome is consistent with experience with providing CIMT for the lower extremities to adult stroke patients for 8 years in our laboratory and for the next 8 years in our outpatient clinic. Our unpublished findings from the 109 stroke patients treated thus far and enrolled under the same lower extremity function inclusion criteria indicate a mean posttreatment improvement on the LE-MAL of 1.8 points ($d'=1.7$). At 4 weeks' follow-up, there was no decrement among the 50 patients who were available for telephone contact. (Further follow-up was not conducted in this population.) There were no adverse events.

The considerable improvements for these real-world activities are consistent with prior CIMT studies in MS and stroke.[15-19] The posttreatment improvements in maximal lower extremity movement ability tested in the laboratory were also large but considerably less than the real-world gains. This too is consistent with earlier studies on CIMT for upper extremity paresis in MS and stroke.[15-19] These findings suggest that the effects of CIMT on functional status for either the upper or the lower extremities do not solely depend on improving maximal limb movement ability. Although further study is required, preliminarily we suggest that the transfer package component of CIMT provides the patient with strategies to overcome problems with transferring treatment gains from the clinic to the real world. These resources apply particularly to the individual challenges in the patient's own home and community, and these strategies may be retained long after discharge, even when there has been disease relapse or gradual progression. A similar basis has been proposed for the long-term reduction of disability scores among patients with chronic back pain after a single course of exercise therapy that was combined with behavioral techniques designed to increase adherence to the exercise regimen in the life situation.[13,14]

Our preliminary finding of long-term transfer of treatment benefits to the real world is thus far unprecedented for physical therapy for MS. However, an alternate treatment approach has recently been implemented in MS with preliminary evidence for real-world improvement in the amount of walking as assessed by

accelerometers worn in the community.[45] The Motl laboratory thus far has tested their method with persons with relapsing-remitting MS and mild ambulatory impairment who have self-reported restrictions in their amount of spontaneous walking. The approach uses a 12-week Internet-based training of self-efficacy and activity goal setting. This method, which in its individualized goal setting uses a technique that is similar to the transfer package, may be ideal for MS patients with mild ambulatory impairments who do not require constant monitoring by therapists, while the CIMT approach would appear to be indicated for patients with more severe locomotor impairments who require hands-on training by a therapist.

It has been suggested that other forms of physical therapy that have been investigated for MS (eg, aerobic exercise, progressive resistance training) can improve health through maintenance of physical function, cardiovascular conditioning, or mood elevation.[8] A CIMT approach might complement such other forms of physical care for persons with MS; the particular treatment regimen would depend in part on the particular patient's personal goals.

Study limitations

Because our results are from a preliminary study of a small patient sample and did not include a control group, many important questions remain that merit further detailed investigations. At present, we cannot indicate the generalizability of our findings to all persons with MS, a disease that by definition affects multiple parts of the central nervous system and hence can result in considerable idiosyncratic differences in neurologic impairment (eg, cognition, vision, pain, fatigue) that may affect treatment compliance and response. MS also presents distinct illness subtypes. Although our study represented patients with major subtypes of MS (relapsing-remitting, primary progressive, secondary progressive), it is possible that larger treatment samples may demonstrate significant differences in outcomes after CIMT according to disease subtype. We also lack a detailed understanding for how treatment effects may have transferred to the community, particularly an objective indication for whether the amount of walking had changed. However, our finding of a very large effect size on the 6MWT is noteworthy, because preliminary findings suggest that the 6MWT predicts the amount of community ambulation in persons with MS as indexed by ankle-worn accelerometers.[46] It would be valuable for future studies of lower extremity CIMT for MS to include accelerometry-based step counts as an outcome. Nonetheless, our current finding of significant improvement on the LE-MAL suggests that the treatment benefit of CIMT pertains to a wide variety of real-world behaviors that involve the lower extremities (eg, climbing into a bed, standing at a sink), and thus not only walking. Further research will also be needed to determine the clinimetrics of the LE-MAL by validating it against other lower extremity motor measures (eg, real-world accelerometry), and the optimal amount of treatment time to be provided in a single course of therapy.

Conclusions

Our study suggests that lower extremity CIMT can be feasible and safe for persons with MS and that it can have real-world benefits on lower extremity use that can last several years after a single course of treatment, even when there is a paradoxical worsening in some MS lower extremity motor abilities. Although much more study will be needed to ascertain the consistency of our initial findings in larger patient samples, our study suggests that it may be possible for persons with MS to experience lasting and significant improvement in a domain of critical importance to quality of life after only a few weeks of treatment. Although our findings suggest that for some patients their real-world lower extremity use may decline several years after treatment, these results invite further investigation to determine whether therapeutic benefits might be maintained or improved by readministering the treatment at yearly or longer intervals; some research suggests that this approach may be beneficial for motor-impaired patients.[47]

Keywords

Mobility limitation; Multiple sclerosis; Physical therapy specialty; Recovery of function; Rehabilitation

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References

1. Zwibel H. Contribution of impaired mobility and general symptoms to the burden of multiple sclerosis. Adv Ther 2009;26:1043-57.
2. Sutliff M. Contribution of impaired mobility to patient burden in multiple sclerosis. Curr Med Res Opin 2010;26:109-19.
3. Smedal T, Myhr KM, Aarseth JH, et al. The influence of warm versus cold climate on the effect of physiotherapy in multiple sclerosis. Acta Neurol Scand 2011;124:45-52.
4. Rampello A, Franceschini M, Piepoli M, et al. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomized crossover controlled study. Phys Ther 2007;87:545-59.
5. Broekmans T, Roelants M, Feys P, et al. Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in multiple sclerosis. Mult Scler 2011;17:468-77.
6. Gijbels D, Lamers I, Kerkhofs L, Alders G, Knippenberg E, Feys P. The Armeo Spring as training tool to improve upper limb functionality in multiple sclerosis: a pilot study. J Neuroeng Rehabil 2011;8:5.
7. Brown TR, Kraft GH. Exercise and rehabilitation for individuals with multiple sclerosis [review]. Phys Med Rehabil Clin N Am 2005;16: 513-55.
8. Dalgas U. Rehabilitation and multiple sclerosis: hot topics in the preservation of physical functioning [review]. J Neurol Sci 2011;311: S43-7.
9. McAuley E, Motl RW, Morris KS, et al. Enhancing physical activity adherence and well-being in multiple sclerosis: a randomised controlled trial. Mult Scler 2007;13:652-9.
10. Bowers TG, Winett RA, Frederiksen LW. Nicotine fading, behavioral contracting, and extended treatment: effects on smoking cessation. Addict Behav 1987;12:181-4.
11. O'Farrell TJ, Choquette KA, Cutter HS. Couples relapse prevention sessions after behavioral marital therapy for male alcoholics: outcomes during the three years after starting treatment. J Stud Alcohol 1998;59:357-70.
12. Ostfeld RJ, Cheung YW, Saal I, et al. A brief office intervention is associated with improved health measures [letter]. Int J Cardiol 2007; 119:239-41.
13. Friedrich M, Gittler G, Halberstadt Y, Cermak T, Heiller I. Combined exercise and motivation program: effect on the compliance and level

of disability of patients with chronic low back pain: a randomized controlled trial. Arch Phys Med Rehabil 1998;79:475-87.
14. Friedrich M, Gittler G, Arendasy M, Friedrich KM. Long-term effect of a combined exercise and motivational program on the level of disability of patients with chronic low back pain. Spine 2005;30:995-1000.
15. Taub E, Miller NE, Novack TA, et al. Technique to improve chronic motor deficit after stroke. Arch Phys Med Rehabil 1993;74:347-54.
16. Gauthier L, Taub E, Perkins C, Ortmann M, Mark V, Uswatte G. Remodeling the brain: plastic structural brain changes produced by different motor therapies after stroke. Stroke 2008;39:1520-5.
17. Taub E, Uswatte G, King DK, Morris D, Crago JE, Chatterjee A. A placebo controlled trial of Constraint-Induced Movement therapy for upper extremity after stroke. Stroke 2006;37:1045-9.
18. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA 2006;296: 2095-104.
19. Mark V, Taub E, Bashir K, et al. Constraint-Induced Movement therapy can improve hemiparetic progressive multiple sclerosis. Preliminary findings. Mult Scler 2008;14:992-4.
20. Shaw SE, Morris DM, Uswatte G, McKay S, Meythaler JM, Taub E. Constraint-induced movement therapy for recovery of upper-limb function following traumatic brain injury. J Rehabil Res Dev 2005; 42:769-78.
21. Taub E, Griffin A, Nick J, Gammons K, Uswatte G, Law CR. Pediatric CI therapy for stroke-induced hemiparesis in young children [review]. Dev Neurorehabil 2007;10:3-18.
22. Taub E, Uswatte G, Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation—a clinical review. J Rehabil Res Dev 1999;36:237-51.
23. Mark VW, Woods AJ, Mennemeier M, Abbas S, Taub E. Cognitive assessment for CI therapy in the outpatient clinic. NeuroRehabilitation 2006;21:139-46.
24. Taub E, Pidikiti RD, Chatterjee A, et al. CI therapy extended from upper to lower extremity in stroke patients. Soc Neurosci Abstr 1999;25:320.
25. Taub E, Uswatte G, Mark V, et al. CI therapy extended from stroke to spinal cord injured patients. Soc Neurosci Abstr 2000;26:544.
26. Pulvermüller F, Neininger B, Elbert T, et al. Constraint-induced therapy of chronic aphasia after stroke. Stroke 2001;32:1621-6.
27. Cherney LR, Patterson JP, Raymer A, Frymark T, Schooling T. Evidence-based systematic review: effects of intensity of treatment and constraint-induced language therapy for individuals with stroke-induced aphasia. J Speech Lang Hear Res 2008;51:1282-99.
28. Meinzer M, Rodriguez AD, Gonzalez Rothi LJ. First decade of research on constrained-induced treatment approaches for aphasia rehabilitation. Arch Phys Med Rehabil 2012;93:S35-45.
29. Roth EJ, Heinemann AW, Lovell LL, Harvey RL, McGuire JR, Diaz S. Impairment and disability: their relation during stroke rehabilitation. Arch Phys Med Rehabil 1998;79:329-35.
30. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 2005;58:840-6.
31. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983;33: 1444-52.
32. Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys 2006; 42:241-55.
33. Morris DM, Taub E, Mark VW. Constraint-induced movement therapy (CI therapy): characterizing the intervention protocol. Eura Medicophys 2006;42:257-68.
34. Taub E, Crago JE, Burgio LD, et al. An operant approach to rehabilitation medicine: overcoming learned nonuse by shaping. J Exp Anal Behav 1994;61:281-93.
35. Uswatte G, Taub E. Implications of the learned nonuse formulation for measuring rehabilitation outcomes: lessons from Constraint-Induced Movement therapy. Rehabil Psychol 2005;50:34-42.
36. Riegle L, Taft J, Morris D, Uswatte G, Taub E. The validity and reliability of the Lower Extremity Motor Activity Log [abstract]. J Neurol Phys Ther 2003;27:172.
37. Haley SM, Jette AM, Coster WJ, et al. Late Life Function and Disability Instrument: II. Development and evaluation of the function component. J Gerontol A Biol Sci Med Sci 2002;57:M217-22.
38. Duncan PW, Wallace D, Lai S, Johnson D, Embretson S, Laster LJ. The Stroke Impact Scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. Stroke 1999;30:2131-40.
39. Phan-Ba R, Pace A, Calay P, et al. Comparison of the timed 25-foot and the 100-meter walk as performance measures in multiple sclerosis. Neurorehabil Neural Repair 2011;25:672-9.
40. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler 2008;14:383-90.
41. Mudge S, Stott NS. Timed walking tests correlate with daily step activity in persons with stroke. Arch Phys Med Rehabil 2009;90: 296-301.
42. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-3.
43. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale: Lawrence Erlbaum; 1988.
44. Fog T, Linnemann F. The course of multiple sclerosis in 73 cases with computer-designed curves. Acta Neurol Scand Suppl 1970;46(Suppl 47):3-175.
45. Dlugonski D, Motl RW, McAuley E. Increasing physical activity in multiple sclerosis: replicating Internet intervention effects using objective and self-report outcomes. J Rehabil Res Dev 2011;48: 1129-36.
46. Weikert ML, Suh Y, Sandroff B, et al. Accelerometry: free-living measure of ambulatory impairments in multiple sclerosis [abstract]. Int J MS Care 2010;12(Suppl 1):73.
47. Rijntjes M, Haevernick K, Barzel A, van den Bussche H, Ketels G, Weiller C. Repeat therapy for chronic motor stroke: a pilot study for feasibility and efficacy. Neurorehabil Neural Repair 2009;23: 275-80.