Improving Ambulation in Multiple Sclerosis

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Abstract

Ambulation is frequently affected by multiple sclerosis (MS), and is one of the most valued neurological functions among individuals with MS. While walking speed and walking distance have been used for decades as indicators of disease progression, other aspects of gait disturbance are not routinely assessed, and the impact of walking limitations on the daily activities and quality of life of patients is not fully understood. Recently, rehabilitation techniques, devices, and medications that aim directly at improving walking performance have been tested in individuals with MS. At the same time, clinician-rated and patient-reported measures of ambulation are being validated in this patient population. As a consequence of these advances, clinicians can draw from a growing body of evidence to enhance decision-making and outcome measurement when trying to help MS patients fight one of the most visible consequences of their disease.

Keywords

Ambulation, multiple sclerosis, rehabilitation, symptom management, outcome measurement

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Persons with multiple sclerosis (PwMS) frequently experience limitations of ambulation in the course of their disease. Not surprisingly, in recent surveys PwMS considered lower extremity function as one of the most important bodily functions,[1] and ranked mobility limitations as the most important factor affecting their quality of life.[2] The impact of MS on ambulation is reflected in the fact that the most commonly used outcome measures in clinical trials of MS disease-modifying therapies, the Expanded Disability Status Scale (EDSS) and the MS Functional Composite (MSFC), include walking performance as one of their main components. There has been an increasing effort to evaluate the effect of traditional interventions on ambulation, and new treatments and devices are being tested or marketed for the specific purpose of improving walking performance in PwMS.

Evaluating Ambulation

The World Health Organization (WHO) defines walking as "moving along a surface on foot, step by step, so that one foot is always on the ground, such as when strolling, sauntering, walking forwards, backwards, or sideways."[3] Walking performance is routinely assessed in the clinical management of PwMS, most often using tests of maximum gait speed in a short distance (e.g. timed 25-foot walk [T25FW],[4] 10-meter walk test). While these tests are easy to administer and sensitive to change, and usually correlate strongly with the EDSS, they do not provide a full evaluation of gait characteristics. The six-minute walk (6MW) has recently been proposed as a measure of walking endurance in MS.[5] The two-minute walk (2MW) may address concerns regarding duration of testing and exertion with the 6MW, but it has not been fully validated in MS. Tests and scales that include an evaluation of balance, such as the Timed Up and Go (TUG) and the Dynamic Gait Index (DGI), are also useful, particularly in a rehabilitation setting. A recent consensus meeting sponsored by the Consortium of MS Centers (CMSC) led to recommendations for the validation of gait measures in MS.[6]

Index scales summarize into a single score various characteristics of walking performance. For example, the scoring of the EDSS takes into account walking distance and the use of assistive devices (particularly for scores between 4.0 and 7.5), and the Ambulation Index (AI) integrates walking speed and the need for assistive devices.[7] The DGI, mentioned above, incorporates walking a short distance on level ground at comfortable speed, climbing steps, and a series of tests that challenge the patient's dynamic balance.[8]

Quantitative and qualitative gait analysis tools provide more detailed information about gait pattern, which can be useful when designing and testing specific interventions on ambulation but are difficult to use in a clinical setting. At the other end of the spectrum, global

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assessments of activity can be obtained via pedometers, accelerometers, and the use of global positioning system (GPS) odometry. While these devices allow measurement of performance in the patient's environment, and over longer periods of time, compared with the short tests used in the office setting, they do not provide detailed information on gait.

More recently, self-report measures such as the MS Walking Scale-12 (MSWS-12) have been validated, allowing integration of the patient's perception of walking performance (and limitations) into outcome measurement.[9] The MSWS-12 has been used in clinical trials of fampridine-SR (see below).[10]

Improving Ambulation

Gait Disorders in Multiple Sclerosis

Ambulation limitations are reported by up to 75% of PwMS.[11] The consequences of limited ambulation include decreased ability to perform activities of daily life, reduced quality of life, and medical complications. For example, the high prevalence of osteoporosis in PwMS has been mostly attributed to decreased mobility,[12] and the combination of osteoporosis and increased risk of falling accounts for a higher incidence of fractures in MS.[13] Therefore, there is a strong incentive to enhance ambulation in PwMS. Specific gait changes observed in PwMS include decreased gait speed, decreased step/stride length, decreased cadence, increased double support time, and increased variability of gait.[14,15] Quantitative gait analysis detects abnormal gait patterns early in the course of the disease, even in the absence of objective functional limitations.[16] There is an increasing body of evidence regarding the effects of various interventions on ambulation in MS.

Disease-modifying Therapies for Multiple Sclerosis

Treatments for MS can have an impact on walking through the reduction of inflammation and axonal damage. Glucocorticosteroids can hasten recovery from exacerbations of MS, although they may not make a difference in long-term outcome.[17] Disease-modifying therapies (DMTs) may slow the accumulation of disability, in part through a reduction in the frequency of exacerbations, which have been shown to constitute the main source of accrual of disability in relapsing MS.[18] However, when a chronic limitation of walking performance is present, the use of DMTs is not generally expected to lead to a sustained improvement of function.

Rehabilitation

Rehabilitative interventions, particularly physical therapy, are usually the first line of defense when attempting to improve ambulation.[19] In an expert opinion paper, the National Multiple Sclerosis Society emphasized the need to consider rehabilitation in MS patients who present with "any functional limitation."[20] The modalities used vary between patients, and may include stretching, strengthening (for example resistance training[21]), aerobic exercise,[22] gait and balance training (including bodyweight-supported treadmill training),[23] and neurodevelopmental theory-based techniques.[24]

Assistive devices such as canes, crutches, or walkers are prescribed to improve the efficiency and safety of walking,[25] but are not always readily accepted by patients, because their use reflects a progression of the disease, may give a feeling of 'giving in,' and can generate a perception of stigma. The most frequently prescribed lower extremity orthotic in MS is the ankle-foot orthosis (AFO), which helps reduce the 'foot drop' due to spastic paresis. The few published studies on the effect of AFO use on gait and balance in MS reflect both a positive and potentially negative impact.[26,27]

Recently, an active orthosis designed to compensate for hip flexor weakness (hip flexion assist orthosis [HFAO]) has shown promising effects on gait performance in a pilot study of 21 MS patients, with significant improvement of performance on a variety of gait tests and significant improvement of hip flexor strength on the limb fitted with the HFAO, suggesting a training effect with brace use.[28]

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Functional electrical stimulation (FES) for spastic paretic foot drop has generated considerable interest in the MS community with the introduction of peroneal stimulation devices (Walkaide®, Innovative Neurotronics Inc., Bethseda MD; NESS L300™, Bioness Inc., San Clarita, CA; Odstock Dropped-Foot Stimulator, NDI Medical, Cleveland, OH). Although promising retrospectively analyzed results were previously published on the effects of peroneal nerve stimulation in MS,[29,30] showing increased walking speed and decreased effort needed to walk, there is a need for prospective randomized controlled studies to better understand the indications for these devices and their advantages over traditional AFOs.

More advanced technologies may facilitate gait training, but have not demonstrated their superiority over more traditional techniques. Lo et al. recently published the results of a randomized cross-over study of robot-assisted gait training (using the Lokomat device) versus bodyweight-supported training on a treadmill in 13 patients with MS. Although there was a significant gain in walking speed, walking distance, and EDSS score after robot-assisted training, there was no statistically significant difference with bodyweight-supported training.[31] Another study showed no significant difference in the effect of robot-assisted gait training versus conventional gait training in 35 MS patients receiving inpatient rehabilitation.[32] Virtual reality improved walking speed and stride length in a study of 16 MS patients with ataxic gait.[33]

Symptom Management

Various symptomatic therapies may have an impact on ambulation in PwMS. We will focus only on treatments for spasticity and fatigue.

Fatigue Management

Fatigue is experienced by most PwMS, is often reported as one of their top complaints, and is a predictor of disability independent of other neurological impairments.[34–36] Fatigue has been defined as "a subjective lack of physical and/or mental energy which is perceived by the individual or care-giver as interfering with usual and desired activities."[37] The pathophysiology of fatigue is not completely elucidated. The effect of MS lesions in the brain, conduction blocks, immune phenomena, and endocrine phenomena have all been considered as possible contributors to fatigue.

Motor fatigue is one aspect of fatigue, and has been defined as the loss of the maximal capacity to generate force during exercise. Schwid et al. observed that MS patients demonstrated more fatigue than healthy controls with ambulation: 60% of their sample of MS patients were unable to walk 500m (while 100% of controls walked 500m), and MS patients demonstrated an average 16.8% slowing during the last 50m of the 500m distance walked, while controls increased their walking speed by an average of 2.0%.[38] Similarly, Goldman et al. found that distance walked and speed during 6MW testing were significantly lower in MS patients compared with controls.[5] Performance on 6MW among MS patients was correlated with the total score and physical sub-scale score of the Modified Fatigue Impact Scale (MFIS), a 21-item self-report measure of fatigue in MS. Finally, controls and MS patients with mild disability slightly increased their walking speed during the last minute of the 6MW, while walking speed decreased in MS patients with moderate or severe disability.

The relationship between fatigue and gait performance is complex, however. For example, Morris et al. reported an increase in patient-reported fatigue between morning and afternoon in MS patients, but no significant decrease in gait performance.[39] Medications commonly used to treat fatigue in MS, such as amantadine and modafinil, have not been shown to improve gait performance. Conversely, fampridine (see below) has a beneficial effect on gait performance, but not on patient-reported fatigue.[40] A study of aerobic exercise on treadmill in 16 MS patients showed improvements in walking speed and walking endurance, but not in fatigue.[41]

Spasticity Management

Spasticity, defined as a velocity-dependent increase in stretch reflex,[42] is frequently experienced by PwMS, and has a significant impact on their quality of life.[43] Clinical practice guidelines for the management of spasticity in MS were published by the CMSC and Paralyzed Veterans of America.[44] Baclofen and Tizanidine are the two most frequently used oral antispasticity agents used in MS. Although these medications have demonstrated efficacy on spasticity-related symptoms in placebo-controlled clinical trials, there are no conclusive data on their functional effects.[45] The same applies to botulinum toxin therapy, which is used for the treatment of focal spasticity in MS and other disorders (although it is not approved for this indication by the FDA): the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) has recently issued a report based on an extensive review of the literature on botulinum toxin therapy for spasticity, which concluded that "Class I placebo-controlled studies have so far failed to demonstrate gains in walking speed."[46] There is increasing interest in using intrathecal baclofen (ITB) therapy to treat severe spasticity in ambulatory patients with MS. Sadiq et al. published a case series including 27 patients with MS and observed no significant loss of walking ability with ITB, but did not report a significant improvement of gait performance.[47] Preliminary results from a prospective uncontrolled study of ITB in ambulatory MS patients showed an improvement of gait speed in some patients.[48] The lack of strong evidence of positive effects should not preclude optimizing spasticity management when trying to improve ambulation in MS, since there have been, to our knowledge, no well-designed published studies carefully evaluating the effect of antispasticity interventions on gait in MS and demonstrating a lack of efficacy. Furthermore, interventions on spasticity have been shown to improve ambulation in other neurological conditions such as spastic hemiparesis due to stroke.

Fampridine (4-aminopyridine or 4-AP)

Fampridine is a potassium channel blocker. The presumed mechanism of action of fampridine is a facilitation of signal conduction along demyelinated axons in the central nervous system (CNS). 4-AP has been available as a compounded medication in the US, and has been proposed initially as a treatment for MS fatigue. A recent publication of a case series of accidental overdose with 4-AP illustrates the risks of compounding.[49] A dose-ranging study of sustained-release fampridine (fampridine-SR) showed a dose-dependent increase in the frequency and severity of adverse events (which included seizures in two subjects at doses of 30 and 35mg twice daily). There was a statistically significant improvement of lower-extremity muscle strength and walking speed (T25FW), but no significant effect on fatigue.[40] The results of a phase III double-blind, placebo-controlled trial of fampridine-SR (10mg bid) were recently published.[10] This study used a responder analysis to evaluate treatment efficacy on walking speed: subjects who exhibited a sustained improvement in walking speed on T25FW testing over the treatment period were considered responders. The proportion of responders was significantly higher in the treatment group (34.8%, versus 8.3% in the placebo group). The average increase in walking speed in the treatment group was 25.2% (versus 4.7% in the placebo group). As per Schwid et al., a 20% change on T25FW testing can be considered clinically significant.[50] Responders also demonstrated a significant improvement on the MSWS-12. Significant improvements in lower-extremity strength were observed in both responders and non-responders who were on active treatment compared with subjects who were on placebo. Interestingly, treatment effects on walking speed were consistent across disease types (relapsing–remitting, secondary progressive, primary progressive, and progressive relapsing). A dose-related increased risk of seizures was again reported. After a second phase III clinical trial, which led to similar findings, a drug application was recently filed with the FDA.

Even though fampridine-SR is not a DMT, it distinguishes itself from common symptomatic medications by its predominant effect on function. Although traditional symptomatic medications may have a positive effect on an individual's ability to function, it is not part of their primary indication, and too often their functional impact has been insufficiently studied. Fampridine-SR could be the first example of a new class of 'function-promoting medications.'

Conclusion

An increasing number of interventions that may enhance ambulation are available to individuals with MS and to the professionals involved in their care. However, choosing the right intervention(s) for a given individual is still a challenge. Further validation of existing ambulation tests and scales is needed, as well as further testing of traditional and newer medications, rehabilitation techniques, and devices. Even though walking speed is important for daily activities, attention should be paid to other aspects of ambulation, such as walking endurance, the energetic cost of walking, and characteristics of gait pattern that may lead to musculoskeletal stress. These are necessary steps to allow PwMS to benefit fully from technological advances in an economic environment in which the cost-effectiveness of these technologies will be increasingly scrutinized. Also, we should always remember that ambulation, while of great importance and value, is only one component of mobility. ■

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