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Effects of lipoic acid on walking performance, gait, and balance in secondary progressive multiple sclerosis

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ABSTRACT

Background: Gait and balance impairment is common in secondary progressive multiple sclerosis (SPMS). Lipoic acid (LA), an over-the-counter antioxidant, is effective in MS animal models and may improve walking speed, but effects on mobility are unreported.

Objective: Examine the effects of 1200 mg daily oral dose of LA versus placebo (PLA) on gait and balance in a 2-year, randomized, double-blind pilot study.

Methods: 134 participants were screened for eligibility before assignment to LA (n = 28) or PLA (n = 26). Included here were, 21 participants with SPMS who took LA (N = 11) or PLA (N = 10) capsules for 2 years (enrolled May 2, 2011 – August 14, 2015) and completed all tasks without the use of an assistive device. Participants completed the Timed Up and Go (TUG) and quiet standing tasks every 6 months while wearing inertial sensors (APDM Opals) to quantify mobility.

Results: LA had a medium effect on time to complete TUG at 2 years (g = 0.51; 95% CI = -0.35, 1.38). In a subset of 18 participants with less disability (EDSS < 6, no use of ambulatory device), turning time was significantly shorter with LA (p = 0.048, Δ= 0.48 s). No differences in balance metrics were found between groups.

Conclusions: LA had an effect on walking performance in people with SPMS, particularly in those with lower baseline disability.

Trial Registration: Lipoic Acid for Secondary Progressive Multiple Sclerosis https://clinicaltrials.gov/ct2/show/NCT01188811?term=spain+lipoic+acid&rank=1 NCT0118881.

1. Introduction

Among physical functions impaired by multiple sclerosis (MS), walking ability is frequently considered most important.[1] Walking impairment is associated with greater use of healthcare resources[2] and increased fall risk. People with MS have larger postural sway and slower walking speed than age-matched control subjects.[3] These impairments are often worse in those with secondary progressive MS (SPMS)[4] than other forms of MS due to cerebellar and vestibular lesions.[5]

Few therapies have been shown to improve or maintain gait and balance in MS. Efficacious treatments might be expected to increase somatosensory conduction speed,[6] or improve the ability of the central nervous system to integrate sensory information.[3] Previous interventions to improve walking in MS have focused on physical training and have rarely been supported by an understanding of the neural mechanisms.[7] Dalfampridine, a potassium channel antagonist, has been shown to improve walking speed in MS, but in clinical trials was deemed effective in only a third of participants.[8] The efficacy of complementary and alternative medicine interventions for gait and balance has also been explored, but there is currently insufficient evidence to support practice recommendations for any modality.[9] Few of the interventions for gait and balance have focused on SPMS, further limiting the applicability and generalizability of these prior findings.[10]

There is a need for therapies that slow the deterioration of gait and balance in SPMS. Lipoic acid (LA) is a readily available dietary supplement that serves as an antioxidant, can stimulate glucose uptake, and supports mitochondrial function.[11] In the animal model of MS, experimental autoimmune encephalomyelitis, LA results in a dose-dependent reduction in disability accompanied by a reduction in

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inflammation, demyelination, and central nervous system (CNS)-entering T cells.[12,13] LA is well tolerated in people with MS and increases serum LA with daily oral doses of 1200 mg.[14] A pilot randomized controlled trial suggested LA improves the T25FW at 2 years.[15] The purpose of this study was to examine the specific gait and balance metrics that contributed to suggested improvement in walking speed in the ambulatory SPMS participants enrolled in the 2-year pilot trial.

2. Methods

2.1. Design

The 2-year study[15] from which participants for this analysis were drawn used a randomized, placebo-controlled, double-blind design. The Veterans Affairs Portland Health Care System (VAPORHCS) and Oregon Health & Science University (OHSU) Institutional Review Boards approved all study methods (FDA IND #110132, NCT0118881).

2.2. Participants

Participants were recruited from the VAPORHCS MS Center of Excellence clinic and the general public. Included participants in this analysis were 40–70 years old, diagnosed with SPMS as defined per the primary paper as "prior RRMS (2005 McDonald criteria), and current SPMS defined by MS disability progression in the absence of clinical relapse during the prior 5 years as determined by the principal investigator (PI) based on history and chart review",[15,16] Expanded Disability Status Scale (EDSS) ≤ 6.0, and able to walk at least 25 feet without an aid. Participants were allowed to choose to take glatiramer acetate, B-interferon, or no disease-modifying therapy during the study. Additional inclusion and exclusion criteria less relevant to the present study analyses are described elsewhere.[15]

2.3. Outcome measures

The expanded Timed Up and Go (TUG) is a task used to assess function and rehabilitation progress in MS and is highly reliable.[17] Participants are seated in a chair and then told to stand up, walk forward 7 m to a tape mark on the floor, make a 180° turn, walk back to the chair, and sit down. Participants completed three different conditions of the TUG. First a TUG was completed at "normal walking speed" (TUG-normal) followed by a TUG done "walking as quickly as possible" (TUG-fast) and then with a cognitive dual-task. The dual-task TUG involved having participants subtract 3 from a starting number (e.g., 139) and continue subtracting 3 from the answer, while completing the TUG "as quickly as possible" (TUG-dual task). Participants were instructed to do their best on both tasks (i.e., walking and subtracting) rather than prioritizing one task and were permitted 30 s rest between each trial.

A quiet standing task measured balance as postural sway. Participants stood as still and as quietly as possible with arms crossed across the chest and feet separated by a template.[18] Quiet standing was done for 30 s under three conditions: eyes open (EO), eyes closed (EC), and eyes closed with a dual-task, i.e. subtracting (EC-dual task) by 3 from a starting number (e.g., 165). Trials were required to last ≥ 5 s to be considered valid and were not conducted if the participant or administrator believed they could not complete them safely and without the use of an assistive device. During all tasks participants wore wireless inertial sensors (APDM Opals) on the ankles, wrists, sternum and lumbar back to quantify movement, as described previously.[18,19] To reduce risk of Type 1 error, the study only tested for group differences in gait variables previously found different in MS (mixed types) from control participants as measured by inertial sensors.[18]

2.4. Procedure

Informed written consent was obtained at the screening visit. The study principal investigator confirmed study eligibility and completed a neurological exam to determine disability level using the EDSS. During this screening visit, participants then completed 3 practice trials of each TUG and sway condition, results of which were not used in the longitudinal data analysis. After the screening visit, participant study treatment was block-randomized according to baseline EDSS (≤ 4.5 vs. > 4.5) by a research pharmacist not otherwise involved in the study. Study drug was from Pure Encapsulations®, who provided capsules containing 600 mg of racemic LA or placebo (PLA; Avicel™, microcellulose crystal and 4.3 mg quercetin) in gelatin capsules. Participants were instructed to take 2 capsules with food daily. Participants and study staff (including primary care physicians and neurologists) were blinded to treatment assignments.

The baseline visit was scheduled within 30 days of the screening visit. Subsequent study visits occurred every 3 months ± 2 weeks until study completion at 2 years for a total of 5 visits that included outcome measures. At each visit, participants completed 3 trials of each TUG and sway task. All tasks were completed in 3 cycles (rather than completing each trial consecutively) to minimize practice effects and fatigue.

2.5. Statistical analysis

Data were analyzed in SPSS version 22 (IBM Corp., Armonk, NY) before the blind was broken. Reliability of each 3 trial TUG and quiet standing condition block was assessed at each time point for each treatment (LA, PLA) using intraclass correlation coefficients with a two-way mixed model for consistency. Reliability was acceptable ($\alpha \geq .85$) at each time point and the median of each trial block was used in subsequent analyses. Data were checked for outliers (> 3 SDs from the mean) and normality using residual and Q-Q plots, and Shapiro-Wilk tests. Outlying values were transformed to the next most extreme score plus one. When data did not meet normality assumptions after the transformation of outlying values for several variables (e.g., jerk, RMS sway), a square root transformation was applied to yield a normal distribution. Mixed models were used to test and estimate treatment X time interactions for each variable, with EDSS score entered as a covariate. Mixed models allow for consideration of the correlation between measures in longitudinal data and can be used with missing data.[20] A subgroup analysis was also conducted that included only participants with EDSS < 6 who were on treatment for the entire 2-year study (n = 18), because baseline disability and adherence could influence the treatment response. A series of one-way ANCOVAs, controlling for group differences in EDSS, tested if change scores (2 years – baseline) were different according to treatment group (LA, PLA). Hedges' *g* and corresponding 95% confidence intervals were calculated using complete data to estimate effect size,[21] which are considered small and medium at values of .20 and .50, respectively.[22] To calculate *g*, the change in the PLA group (baseline – post) was subtracted from the change in the LA group, and divided by the pooled standard deviation from baseline.

3. 3 Results

Demographic characteristics of participants that completed the full study are provided in Table 1. Treatment compliance (measured by pill counts) was high (> 80%) and not different between LA and PLA. 25 participants were assigned to treatment (and included in the mixed models), with 21 completing the full 2-year study.

3.1. Timed up and go

There were no statistically significant treatment X time interactions (all $p \geq 0.88$) for time to complete the TUG in any of the 3 conditions. However, LA had a small effect on time to complete the TUG-fast at 6 months ($g = 0.23$; 95% CI = -0.62, 1.09) that increased by 2 years ($g = 0.51$; 95% CI = -0.35, 1.38). The effect at 2 years equates to over a