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ORIGINAL ARTICLE

Home Aerobic Training for Cerebellar Degenerative Diseases: a Randomized Controlled Trial

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Abstract

Balance training has shown some benefits in cerebellar ataxia whereas the effects of aerobic training are relatively unknown. To determine whether a phase III trial comparing home aerobic to balance training in ambulatory patients with cerebellar ataxia is warranted, we conducted a single-center, assessor-blinded, randomized controlled trial. Nineteen subjects were randomized to aerobic training and 17 subjects to balance training. The primary outcome was improvement in ataxia as measured by the Scale for the Assessment and Rating of Ataxia (SARA). Secondary outcomes included safety, training adherence, and balance improvements. There were no differences between groups at baseline. Thirty-one participants completed the trial, and there were no training-related serious adverse events. Compliance to training was over 70%. There was a mean improvement in ataxia symptoms of 1.9 SARA points (SD 1.62) in the aerobic group compared to an improvement of 0.6 points (SD 1.34) in the balance group. Although two measures of balance were equivocal between groups, one measure of balance showed greater improvement with balance training compared to aerobic training. In conclusion, this 6-month trial comparing home aerobic versus balance training in cerebellar ataxia had excellent retention and adherence to training. There were no serious adverse events, and training was not interrupted by minor adverse events like falls or back pain. There was a significant improvement in ataxia symptoms with home aerobic training compared to balance training, and a phase III trial is warranted. Clinical trial registration number: NCT03701776 on October 8, 2018.

Keywords Spinocerebellar degeneration · Ataxia · Aerobic exercise · Balance training

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Introduction

Cerebellar ataxias are a group of disorders that result from cerebellar degeneration and cause a lack of coordination and poor balance [1]. There are over 40 distinct types, many of which affect proteins with unknown functions [2]. The onset of ataxia typically occurs in mid-adulthood, but manifestation in childhood or old age can occur [3]. The diseases are devastatingly debilitating with many individuals requiring wheelchairs for mobility within 10 years from initial diagnoses, and most disease types lead to premature death [4]. Although some clinical trials are underway, there are currently no Food and Drug Administration (FDA)–approved medications for these disorders. [5]

With no disease-modifying medications currently available, most guidelines for cerebellar ataxia recommend balance training so that individuals improve motor skills and maintain their ability to perform activities of daily living [6, 7]. Although several studies have investigated the impact

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of balance training on cerebellar ataxias, most have small sample sizes (ranging from 8 to 42 participants) [8–13]. Moreover, conflicting results have been reported, most likely due to the different training protocols implemented during each study, making interpretation of the benefits of balance training difficult. However, a few studies have suggested that balance training improves symptoms of individuals with cerebellar degeneration if the training is adequately challenging [9, 14–16]. In these studies, improvements in ataxia symptoms ranged from 1.0 to 2.8 points on the Scale for the Assessment and Rating of Ataxia (SARA), a 40-point scale with higher scores indicating more severe ataxia and a minimal clinically significant difference represented by 1.0 point. [9–16]

The benefits of aerobic training in individuals with cerebellar ataxia have been less well studied. After promising results in animals, the first study examining aerobic training in humans with cerebellar degeneration showed minimal benefits [17]. Using the International Cooperative Ataxia Rating Scale (ICARS), an assessment with a minimal detectable change score of 1.96 points [18], a 4-week cycling program caused an improvement of only 2.2 points in participants with spinocerebellar ataxias. Moreover, there were no significant improvements in gait speed or endurance as measured by a 10-min walk test [17]. However, participants were not provided a structured exercise program, and the training consisted of only three, 15-min sessions per week for the 4 weeks. Hypothesizing that a larger dose of training could be beneficial, our research group devised a study examining the ability of individuals with cerebellar degeneration to perform rigorous aerobic training, defined as 65–80% of their maximum heart rate as measured by cardiopulmonary exercise testing. In this prior, small phase I pilot study, individuals with cerebellar ataxia were able to safely perform rigorous aerobic exercise [19, 20]. Moreover, although not powered to detect differences between groups, individuals with cerebellar degeneration who performed home aerobic or balance training for 1 month had improvements in gait, balance, and ataxia symptoms. [19, 20]

The mechanisms of how aerobic and balance training improve symptoms in cerebellar ataxia are still being investigated. Both training regimens may improve compensation for deficits in individuals with degenerative cerebellar diseases [20]. For example, aerobic training may allow individuals to combat fatigue-induced worsening of ataxia, or increase leg strength, improving overall stability [20]. Balance training may help teach an individual with cerebellar degeneration to better utilize afferent information to perceive movement [21], or it may cause neuroplastic changes outside the cerebellum to allow better compensation of deficits [22–24]. Alternatively, aerobic training may induce the degenerating cerebellum to undergo neuroplastic changes [21]. Support for this theory comes from studies with healthy individuals that shows aerobic training increases functional connectivity with the cerebellum [25–27]. Moreover, certain aerobic tasks, such as drumming, have been shown to increase the cerebellar size of healthy individuals. [28].

Here, we report the results of a phase II randomized controlled study comparing home balance versus aerobic training in individuals with cerebellar ataxias. This study is different from our previous studies in the following ways: (1) a sample size calculation was not done in the prior study, and it was not powered to detect differences between aerobic and balance training groups [20]. A sample size calculation was done in this current study, and enough participants were recruited to adequately detect differences between training groups. (2) A main limitation of the prior study was that individuals only performed aerobic training for 1 month making it difficult to determine adherence to training and trial drop-out rates for longer studies [19, 20]. The current study had individuals perform training for 6 months, giving a better estimate for participant retention and compliance to training in future studies.

The goal of this phase II study was to determine if a more definitive trial with more participants is warranted. We anticipate, like in our smaller pilot study, that both training methods will improve ataxia symptoms, but that the aerobic training will cause a larger clinically significant improvement in ataxia symptoms when compared to balance training.

Methods

Study Design and Participants

This was a stratified, single-center, assessor-blinded randomized controlled trial with equal allocation between groups. The study ran from January 2020 until June 2021. The study design consisted of initial assessment, followed by group randomization, 6 months of either home balance or aerobic training, and finally post-training assessment. All assessments were conducted at Columbia University Irving Medical Center. Individuals with cerebellar ataxias were recruited from the Ataxia Clinic at the Neurological Institute at New York Presbyterian-Columbia University Irving Medical Center. Inclusion criteria for the study consisted of the presence of cerebellar atrophy on magnetic resonance imaging, prevalence of ataxia on clinical exam, and SARA sitting sub-score less than or equal to 1 (able to sit safely and use a stationary exercise bike) [29]. Participants were excluded if they had other neurological diseases, cognitive impairment (i.e., Mini-Mental State exam [30] score < 24), heart disease, joint pain, inability to exercise, and SARA walking sub-score > 6 (inability to walk without assistance from another person), or if they were medically unstable. Subjects with a variety of cerebellar ataxia types, including

idiopathic and multiple system atrophy-cerebellar type, were allowed to participate in the study as long as their predominant neurological deficit was ataxia. Participants were classified as having idiopathic cerebellar ataxia if they had cerebellar atrophy on MRI and declined genetic testing or no known genetic mutation was found with genetic testing. Clinically, all participants had evidence of at least mild ataxia (SARA score > 3) [31] for more than 3 months.

Study Protocol Approval, Registrations, and Patient Consents

This study was conducted in accordance with the Declaration of Helsinki. All participants gave informed written consent according to the human study guidelines of the Columbia University Institutional Review Board, reference number AAAS0414. The study is registered at www.clinicaltrials.gov, number NCT03701776.

Sample Size

Using the effect size and standard deviations from the phase I trial, we calculated that 17 participants would be required in each group to have 80% power to detect changes in ataxia severity between balance and aerobic training [19, 20]. In order to ensure 17 individuals were enrolled in each group, 36 subjects were recruited for this study.

Randomization

The study statistician (S.L) generated the randomization sequence. A stratified randomization, with a 1:1 allocation ratio and varying block sizes of 4 and 6, was used to assign subjects to treatment. Participants were stratified by disease severity (mild [SARA score < 10] and severe [SARA score ≥ 10]) [31]. The randomly generated treatment allocations were then delivered to the study team in sealed opaque envelopes.

After the initial assessment, so that SARA scores were known for randomization, participants were allowed to open the sealed envelopes to determine treatment allocation. The assessors who performed the outcome assessments were blinded to the group allocation. Participants could not be masked to group allocation because the intervention involved home exercise, but allocation was masked from the trial statistician until the database was closed. Subjects were explicitly instructed and reminded not to reveal their treatment allocation to the outcome assessors. Assessor blinding was further maintained by video recording outcome assessments and scrambling the order so that the outcome accessor would not know if the assessment was done before or after training.

Interventions

Aerobic Training

Participants assigned to aerobic training were provided with a ProGear 225 Folding Magnetic Upright Exercise Bike with Heart Pulse (Beverly Hills, CA). At the initial assessment, subjects were given written instructions on how to perform aerobic exercise. Instructions consisted of a 5-min warm-up period, 30 min of training at target heart rate, and 5-min cool-down. Participants were also encouraged to perform static stretch exercises to the quadriceps, hamstrings, and calves before and after training to prevent injury. Participants were asked to conduct cycling five times per week for 6 months. In previous studies, cardiopulmonary exercise testing (CPET) was used to guide the prescription of exercise intensity. However, due to hospital policy during the COVID-19 pandemic, CPET testing was not possible. Instead, participants were asked to start training at 65% of their maximum heart rate based on their age [32]. Participants were then called every 2 weeks to discuss training. If individuals were unable to hit training heart rate goals, the intensity was decreased by 5%. If participants achieved training heart rate goals, they were asked if the training was easy, moderate, or hard. If training was considered moderate or hard, participants were instructed to maintain the same exercise intensity for the next 2 weeks. If training was considered easy, the participants' heart rate goal was increased by 5% up to 80% of the age-predicted maximum heart rate. [33].

An exercise log was provided for participants to record the dates and duration of exercise. Additionally, participants were asked to record average heart rate, maximum heart rate, Borg score, and cycling distance. Average training heart rate, training intensity, and Borg score were determined for the entire training program for each individual using these exercise logs, and participants were considered compliant with training goals if they achieved 80% of goals (training at least 24 min per session, 4 times per week, at 65% maximum heart rate) [33, 34]. Biweekly phone calls were performed to answer questions, allow for the report of any adverse events, and encourage participants to continue exercise.

Balance Training

Participants assigned to the balance training group were given a manual consisting of three levels of exercises: easy, moderate, and hard (Supplementary Fig. 1). The manual consists of pictures and explanations of how to perform each exercise. At the initial visit, a demonstration of the exercises was provided, and participants were given time to ask questions.

For training, participants were instructed to perform 30 min of exercise, 5 times per week for 6 months.

Specifically, subjects were asked to complete six different exercises for a duration of 5 min each per session. They were instructed to constantly vary exercises to increase balance challenge.

An exercise log was provided for participants to enter the dates and duration of exercise. Participants were also asked to record the level of balance challenge (1–10 scale with 10 being of highest difficulty) and confidence in maintaining balance (0–100% with 0 representing no loss of balance during training and 100% indicating a fall). Biweekly phone calls were performed to address questions regarding exercises, allow for the report of adverse events, and encourage participants to continue exercise. Participants were also asked about their average level of balance challenge for the week. If the number was less than 6, they were asked to perform more challenging exercises, such as going from easy level to moderate.

Outcome Measures

SARA

The primary clinical outcome measure was the SARA, a 40-point scale that evaluates the degree of ataxia. A score of zero indicates no signs of ataxia whereas a score of 40 indicates the most severe ataxia. The scale has excellent test–retest reliability (correlation coefficient = 0.90), inter-rater reliability (correlation coefficient = 0.98), and internal consistency [31]. Recent clinical trials have used a reduction of 1.0 point on the SARA scale as a clinically meaningful difference (https://clinicaltrials.gov/ct2/show/NCT03347344?term=riluzole&cond=ataxia&draw=2&rank=2) [37].

The SARA was performed by a trained clinician and video-recorded with the participant's consent. Video recordings of the SARA were then scrambled and presented to the outcome accessor in a random order so that they would not know if the test was performed before or after training. Thus, the outcome accessor for SARA was blinded to both participant allocation and timing of assessment.

Balance and Gait

To monitor balance and gait, three tests were performed. Gait speed was determined by asking participants to walk as fast as possible on a 10-m runway three times, and the times were averaged. The Timed Up and Go (TUG) test was also performed three times, and the reported time is the average of these three trials [38]. Finally, participants performed the Dynamic Gait Index (DGI) using the established protocol as a measure of balance [39]. Scores on the DGI range from 0 to 24 with lower scores indicating more severe problems with balance and increased risk of falling. Although not determined on individuals with spinocerebellar ataxia, a minimal clinically important difference of 1.9 points was determined for community-dwelling older adults. [40].

Adverse Events

Participants were instructed to call the research team if they experienced any adverse events during the trial. Participants were also asked about any problems or adverse events at each 2-week phone call regarding training. In particular, participants were asked about any falls, back pain, or COVID-19 infection. All adverse events were documented for severity, duration, and if the event impacted training protocols.

Statistical Analysis

For comparisons of demographic data and the baseline outcome measures between the two groups, we used the two-sample *t* test and the chi-squared test as applicable.

All analysis was done under intent-to-treat principles. The primary (SARA) and secondary (walking speed, TUG, Dynamic Gait Index) outcomes were analyzed using a mixed-effect model. Each mixed-effect model includes the outcome as the dependent variable and group (two levels: aerobic training vs. balance) and time (two levels: pre-training vs. post-training) and the interaction effect between group and time as the fixed effects. A within-subject correlation was accounted by adding a random intercept. For significant time by group interaction, the within-group changes were estimated using the least squared mean. The mixed-effect model allows missing values under the missing-at-random assumption. To ensure the missing-at-random assumption, we compared the demographics and baseline clinical characteristics between participants who dropped and those who completed the trial. We also performed the mixed-effect models only, including completers as a sensitivity analysis. Finally, to guide future studies and meta-analyses, we reported the Cohen's *d* that indicates the standardized difference between two means relative to their standard deviation. For all hypotheses, two-tailed tests were performed at the 5% significance level. Pass Software (v19.0.3) was used to estimate sample size for future studies setting power to 0.8 and α at 0.05.

Results

Figure 1 shows the consort flow diagram. Fifty-seven patients were selected for trial screening from the Ataxia Clinic with 21 subjects excluded. Seven participants did not meet inclusion criteria (most often the participants were not able to safely get on and off a stationary exercise bike), and 14 participants declined participation with distance

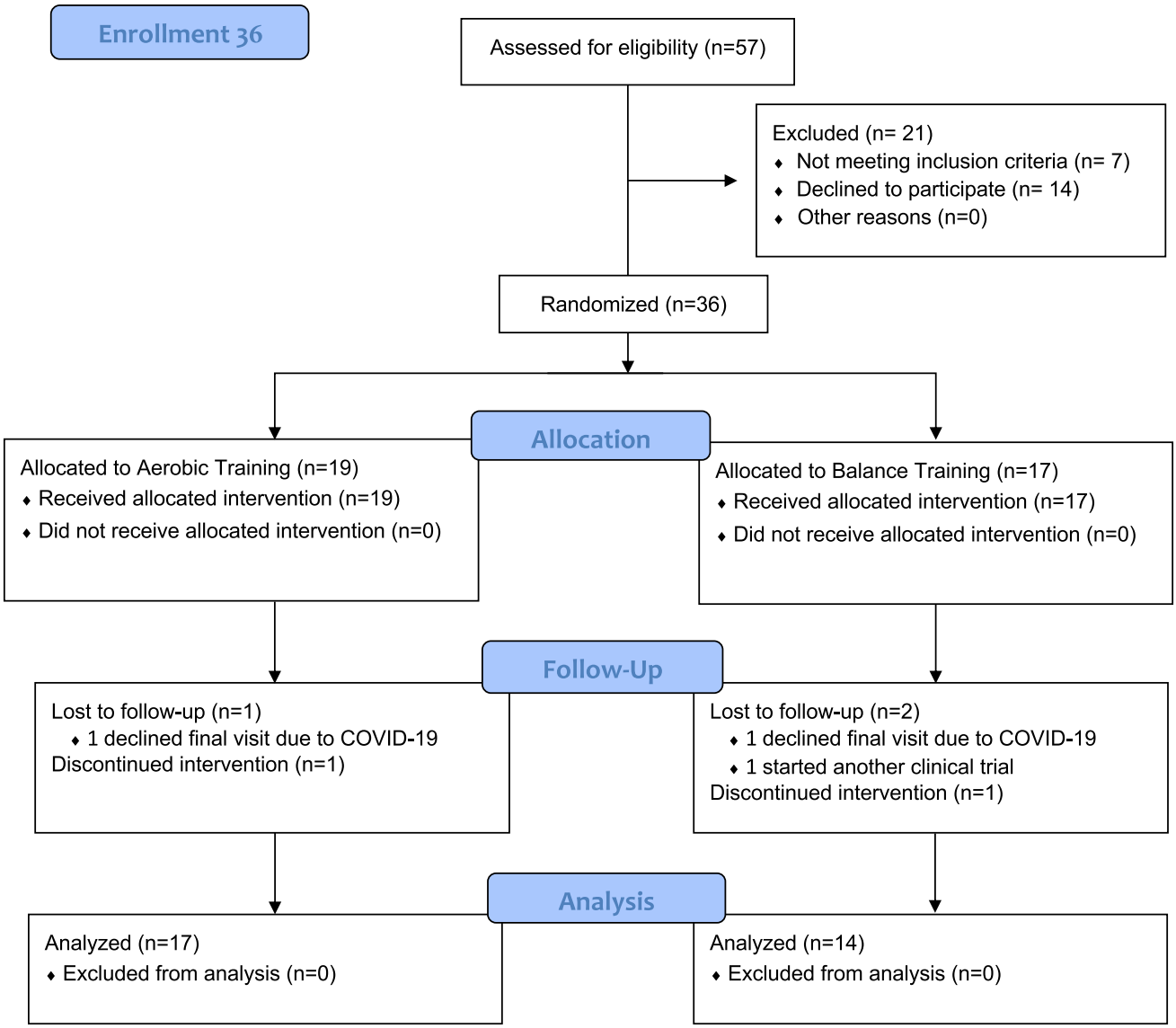

Fig. 1 Consort flow diagram

from the study center as the most frequently cited reason. Thirty-six participants were randomized in the trial. Of the 19 randomized to aerobic training, 89% (17) completed the study whereas 82% (14/17) completed the trial in the balance group. Baseline characteristics were similar between groups, including disease type, age, baseline SARA scores, and medication use (Table 1). [41, 42]

Table 2 shows the adherence of participants to training frequency, duration, and intensity. In the aerobic group, 76% of participants achieved all training goals whereas 71% achieved all goals in the balance group. For both groups, training frequency was the most difficult for participants to attain.

Table 3 shows the minor and severe adverse events that occurred while participants conducted the training. There were no training-related severe adverse events. In the aerobic training group, the most common minor adverse event was back pain (4 episodes of back pain in 2 different participants). Back pain resolved with non-prescription medication and did not impact training. The most common minor adverse event in the balance group was falls (4 falls from 3 different participants), which were clearly defined to participants as a fall to the ground. Falls typically occurred when participants lost balance while using a stability ball. No injuries were sustained from the falls. There were three individuals who developed COVID-19 infection during the trial. Two individuals only had minor symptoms and did not require hospitalization. After 10 days, both of these individuals were able to restart training. The other individual was not hospitalized initially with COVID-19 infection, but

Table 1 Comparison of group demographics

	Aerobic	Balance	Total	*P*-value
Number of patients	19	17	36	
Age in years (SD)/range	54.9 (16.4)/24–79	51.1 (13.3)/25–72	53.1 (14.9)/24–79	0.46
Disease duration in years (SD)	8.2 (7.0)	7.8 (4.4)	8.0 (5.9)	0.81
Female/male	8/11	8/9	16/20	0.77
MSA-C/SCA/idiopathic	3/5/11	3/5/9	6/10/20	0.96
Using riluzole	11	10	21	0.95
SARA (SD)	11.7 (5.5)	11.3 (3.7)	11.5 (4.7)	0.83
Walking speed in m/s (SD)	0.85 (0.28)	0.85 (0.32)	0.85(0.30)	0.97
TUG in seconds (SD)	17.0 (7.0)	17.7 (8.3)	17.3 (7.5)	0.79
Dynamic Gait Index (SD)	15.8 (4.4)	14.4 (4.1)	15.2 (4.3)	0.32

Table 2 Adherence to training program

Training group	Met training frequency goal (Y/N)	Met training duration goal (Y/N)	Met training intensity goal (Y/N)	Hit all target training goals (Y/N)
Aerobic	14/3	16/1	16/1	13/4
Balance	10/4	13/1	14/0	10/4

Participants were considered adherent to exercise training if they trained at 80% of their training frequency, duration, and intensity goals. Participants met the frequency goal if they trained at least 4 times per week. Participants met the duration goal if they trained at least 24 min per session. In the aerobic group, participants met the intensity goal if they trained at 65% of the maximum heart rate determined by age. In the balance group, participants met the intensity goal if their average balance challenge per session was at least a 6. There was no statistical difference ($p > 0.05$) between groups

Table 3 Adverse events

	Aerobic training	Balance training
Minor adverse events		
Related to exercise	5 (29%)	4 (29%)
Unrelated to exercise	3 (18%)	2 (14%)
Severe adverse events		
Related to exercise	0 (0%)	0 (0%)
Unrelated to exercise	0 (0%)	1 (7%)
Most common adverse events		
Back pain	4 (24%)	1 (7%)
Falls*	0 (0%)	4 (29%)
Palpitations	1 (6%)	0 (0%)
Other joint pain	1 (6%)	1 (7%)
COVID-19 infection, not hospitalized	2 (12%)	0 (0%)
Severe adverse events		
COVID-19 infection, hospitalized	0 (0%)	1 (7%)

Number of participants in each group who had minor adverse or severe adverse events. *There was a statistical difference ($p = 0.02$) between aerobic and balance groups for falls. There was no statistical difference ($p > 0.05$) for all other adverse events

subsequently developed idiopathic thrombocytopenia purpura (ITP) requiring a short hospital stay. This individual was able to restart training but had to take 1 month off from training due to illness.

Outcomes

Table 4 shows the effects of aerobic and balance training on ataxia severity and measures of balance and gait. There was a mean improvement in ataxia symptoms of 1.9 SARA points (SD: 1.62, 95% CI [−2.7, −1.2]) with aerobic training, which was statistically significant ($p < 0.0001$). Although there was a mean improvement in ataxia symptoms of 0.6 points (SD: 1.34, 95% CI [−1.5, 0.1]) for the balance group, pre- and post-training values were not statistically different ($p = 0.09$). Comparing groups, there was greater improvement in ataxia symptoms observed with aerobic training compared to balance training ($p = 0.025$; Cohen's $d = -0.84$). Figure 2 shows the boxplot for post–pre change scores for SARA.

There was a mean statistically significant ($p = 0.002$) increase in gait speed after aerobic training of 0.12 m/s (SD: 0.16, 95% CI [0.05, 0.18]). Although gait speed was not statistically increased with balance training ($p = 0.07$), there was no statistical difference observed between groups ($p = 0.38$; Cohen's $d = 0.34$). There was a statistically

Table 4 Comparison of outcomes between aerobic and balance training groups

	Aerobic training			Balance training			Treatment effect	
	Baseline assessment	Post-training assessment	Difference[1] [95% CI]	Baseline assessment	Post-training assessment	Difference[1] [95% CI]	Cohen's *d*	Estimates[2]
SARA	11.8 (5.5)	9.9 (5.0)	−1.9 [−2.7, −1.2] **(*p* < 0.0001)**	11.6 (3.6)	11.0 (3.8)	−0.6 [−1.5, 0.1] (*p* = 0.09)	−0.84	−1.3 [−2.3, −0.2] **(*p* = 0.025)**
Walking speed in m/s	0.80 (0.26)	0.92 (0.35)	0.12 [0.05, 0.18] **(*p* = 0.002)**	0.82 (0.26)	0.89 (0.30)	0.07 [0.01, 0.15] (*p* = 0.07)	0.34	0.05 [−0.06, 0.15] (*p* = 0.38)
TUG in seconds	17.4 (7.3)	15.9 (8.0)	−1.3 [−2.5, −0.2] **(*p* = 0.02)**	16.6 (8.2)	15.3 (7.1)	−1.3 [−2.6, 0.05] **(*p* = 0.043)**	−0.02	0.0 [−1.7 − 1.7] (*p* = 0.98)
DGI	16.0 (4.3)	17.3 (4.4)	1.1 [0.2, 1.9] **(*p* = 0.014)**	14.2 (4.0)	16.8 (4.0)	2.6 [1.6, 3.5] **(*p* < 0.0001)**	0.90	1.5 [−2.7, −0.3] **(*p* = 0.017)**

Data shown is mean (SD). [1]Difference represents the least means square difference (pre-post) with *p*-value. Effect size is reported by Cohen's *d*. [2]Treatment effect was estimated as the group × time interaction in the mixed-effect models. Abbreviations: *SARA* Scale for the Assessment and Rating of Ataxia, *TUG* Timed Up and Go, *DGI* Dynamic Gait Index, *CI* confidence interval

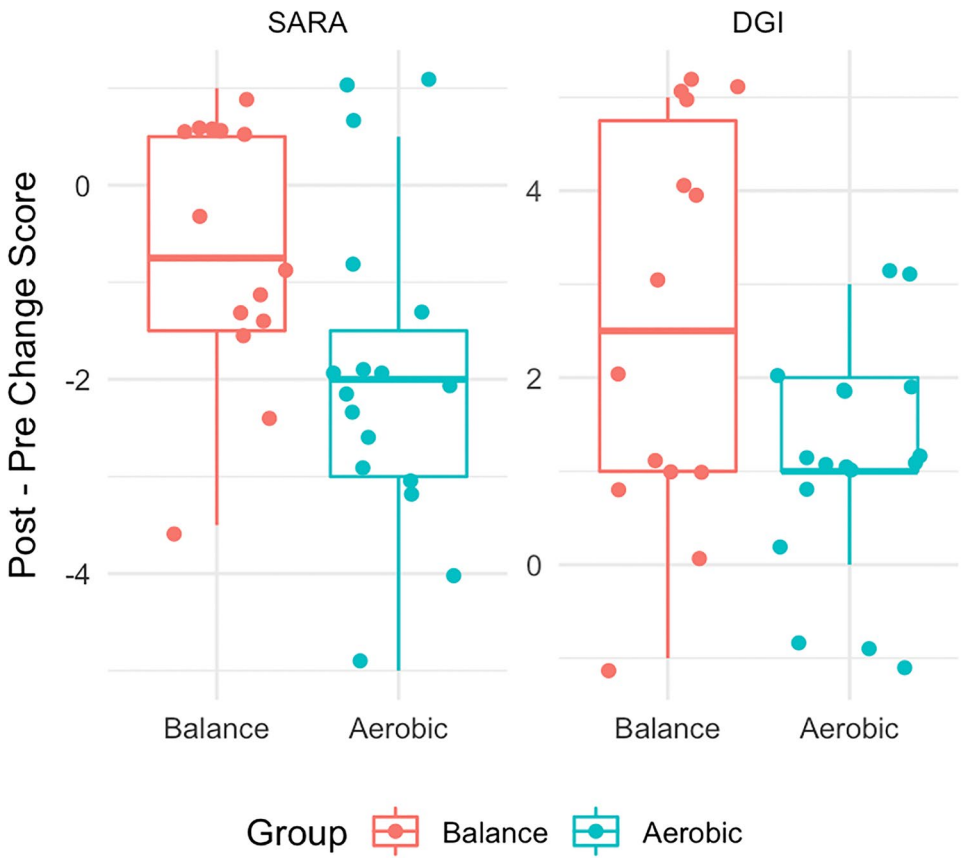

Fig. 2 Box plot for post–pre change scores for SARA and DGI. Abbreviations: SARA, Scale for the Assessment and Rating of Ataxia. DGI, Dynamic Gait Index

significant improvement in TUG times after both aerobic and balance training ($p = 0.02$ and $p = 0.04$, respectively), but there was no difference observed between groups ($p = 0.98$; Cohen's $d = -0.02$). Finally, although there was a statistically significant improvement in DGI scores after aerobic training ($p = 0.02$), there was a larger improvement in DGI scores after balance training when compared to aerobic training ($p = 0.017$; Cohen's $d = 0.90$). Figure 2 shows the boxplot for post–pre change scores for DGI.

Using the effect size and standard deviations from this study, we calculated that 24 individuals would be required in each group to have 80% power to detect changes in ataxia severity between balance and aerobic training. Using a retention rate of 80% and an exercise adherence rate of 70%, 43 individuals would be required per group in a more definitive future phase III trial.

Discussion

This paper reports the findings of a phase II randomized controlled trial comparing a 6-month home aerobic training program to balance training in individuals with degenerative cerebellar diseases. Compared to prior studies with shorter training duration and fewer participants, this study provides better estimates of treatment effect, participant retention, and adherence to training for sample size calculation of future studies. The retention of participants in the study was high for an exercise study (greater than 80%) as was adherence to training (greater than 70%). Exercise retention is typically low with as many as 50% of individuals who start an exercise program dropping out within 6 months. [43] Even in research studies with carefully designed and implemented aerobic training programs, attrition rates remain high at 25–50%, and participants who do complete the training typically have poor adherence [44–46]. There are a few possibilities for the high retention and adherence to training in this study. First, these diseases are debilitating with no effective treatments. Thus, the study population is extremely motivated with almost no other options for treatment. Second, the study was conducted during the COVID-19 pandemic, and adherence to home training may be artificially elevated as participants were largely homebound with few other activities available to them. Indeed, multiple participants reported that they trained often because of more time at home and fewer outside commitments. Retention and adherence may also have been improved due to the biweekly phone calls urging participants to continue with the training and answering any questions.

In terms of adverse events, it was encouraging that there were no serious adverse events caused by training in either group. In the aerobic group, the most common minor adverse event was episodes of back pain. These episodes were relieved with over-the-counter medications and did not impact training. When reported, individuals were instructed to ensure that their bike seat was at the appropriate level, and back pain symptoms typically improved when the individual raised the seat. For the balance group, the most reported minor adverse event was falls, but no injuries were sustained from these events. The typical fall was off the stability ball from the sitting position. Participants reported being apprehensive with some exercises because they were afraid of falling but were encouraged to challenge their balance to the best of their ability. Indeed, all fourteen participants in the balance group were able to achieve a balance challenge score of at least a 6 without having many falls.

An unexpected result seen from this trial was that the balance group had a statistically significantly greater improvement in DGI score when compared to aerobic training ($p = 0.017$; Cohen's $d = 0.90$). In prior studies with shorter duration training, differential improvement in DGI scores between balance and aerobic training groups was equivocal. One possible explanation for this finding is that there may be a learning effect in balance training. Some of the more difficult exercises in the home balance training program mimic tests done during the DGI. For example, there is an exercise to look and talk with a friend or family member while walking, which is similar to the DGI test of walking while turning head left and right. This learning effect may not have been present in the earlier, shorter study as participants may not have performed these more challenging exercises on a regular basis [20]. Also consistent with a learning effect, other measures of balance, like the TUG, showed equal improvement between aerobic and balance training groups.

In terms of ataxia severity, although there was an improvement in ataxia severity after balance training (Δ SARA $= -0.6$), the result was not statistically significant ($p = 0.07$). This result is inconsistent with some other studies conducting balance training in individuals with cerebellar degradation [8, 10–12]. However, in these studies, training was supervised. In other studies where balance training was not supervised, improvements in ataxia severity were less robust [9, 13, 47]. In two studies, improvements in ataxia severity were initially seen after supervised balance training, but then ataxia declined back to baseline with home training [9, 47]. In another study, home balance training showed improvements in gait speed and balance, but not ataxia severity [13]. One possibility for this finding is that individuals have difficulty adequately challenging themselves at home as opposed to when training is supervised [9, 14–16]. Thus, even though we encouraged participants in the balance group to challenge themselves, they may have had a difficult time doing so without the aid of an experienced therapist.

For the aerobic group, there was a mean improvement in SARA of 1.9 points after training. Although the minimally clinically important difference for the SARA is unknown, researchers have used a change of 1.0 points as clinically significant. Thus, the improvement seen with aerobic training would be considered clinically meaningful.

When comparing groups, aerobic training caused a statistically significantly greater improvement in SARA than balance training, and this training effect is considered large (Cohen's $d > 0.8$). Thus, for a phase III trial, a sample size of 86 participants was calculated using the results of this trial. This sample size is feasible for a multi-center trial, and it

may even be possible to conduct a trial focusing on one or two specific types of cerebellar degeneration.

There are a variety of limitations to this study. First, to ensure enough participants, individuals with a variety of different causes of cerebellar degeneration were enrolled. With the relatively small sample size, we could not determine if certain types of cerebellar degeneration respond better to training than others. Another limitation was that the training was conducted during the COVID-19 pandemic. As a result, CPET testing was not performed to help tailor the aerobic exercise program. Moreover, adherence to training may have been artificially high due to the pandemic lockdown. In addition, adherence to training was monitored by self-report, which may also cause inflated adherence training rates. Another limitation was that the balance and aerobic training programs were done in separate groups. There have been multiple studies showing that aerobic exercise can prime the brain for improved rehabilitation [48–51]. Thus, this study did not address whether a combination of aerobic and balance training may be more beneficial than either training alone. Finally, this study does not address the mechanisms underlying the training effects. These questions are areas of future study.

Conclusions/Implications

Rigorous aerobic training appears safe in individuals with cerebellar ataxia, and there was high retention and adherence to training in this trial. Home aerobic training may be more beneficial in improving ataxia than balance training in individuals with cerebellar ataxias. However, balance training may be more beneficial in improving measures of balance than aerobic training. A future phase III trial comparing home aerobic and balance training is warranted and such a study is feasible with an estimated 43 participants needed in each group.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12311-022-01394-4.

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Declarations

Competing Interests The authors declare no competing interests.

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