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Phase I randomized single-blinded controlled study investigating the potential benefit of aerobic exercise in degenerative cerebellar disease

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Abstract

Objectives—To investigate whether people with cerebellar degeneration can perform rigorous aerobic exercise and to assess the clinical impact of training.

Design—Randomized single-blinded controlled, feasibility study comparing aerobic training to no training.

Setting—Home intervention, assessments conducted at an academic medical center.

Subjects—Twenty individuals with cerebellar degeneration caused by a range of genetic disorders.

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Supplemental material

Supplemental material for this article is available online.

Intervention—Aerobic training consisted of four weeks of stationary bicycle training, five times per week for 30-minute sessions. Intensity ranged from 65% to 80% of the participant's maximal heart rate determined during cardiopulmonary exercise testing.

Main measures—Primary outcome measure was change in the Scale for the Assessment and Rating of Ataxia scores. Recruitment rate, adherence, drop-out, and adverse events were also determined. The treatment was considered technically feasible if participants achieved target training frequency, duration, and intensity.

Results—The 20 participants mean age was 50 years (standard deviation 15.65 years) and average Scale for the Assessment and Rating of Ataxia score was 9.6 (standard deviation 3.13). Ten participants were randomized to aerobic training and 10 to no training. Seven participants in the aerobic group attained target training duration, frequency, and intensity. There was a mean reduction in ataxia severity of 2.1 points (standard deviation 1.26) with four weeks of aerobic training, whereas ataxia severity increased by 0.3 (standard deviation 0.62) in the control group over the same period. Walking speed, balance measures, and fitness also improved in individuals who performed aerobic exercise.

Conclusions—Rigorous aerobic training is feasible in people with cerebellar degeneration. Improvements in ataxia, balance, and gait are promising.

Keywords

Ataxia; rehabilitation; spinocerebellar degeneration; aerobic exercise; treatment outcome

Introduction

Degenerative cerebellar disease comprises a group of heterogeneous disorders marked by impaired balance, loss of coordination, and gait deficits. Without disease-modifying medications,¹ rehabilitation is the mainstay of treatment to improve motor skills and functional performance. Research has focused primarily on balance training for these diseases with several articles published.^{2–6} Although results vary, balance training appears to improve ataxia severity if there is adequate balance challenge.^{3,5}

The effects of aerobic training in degenerative cerebellar disease, however, are relatively unknown with only two human studies published. In the first study, 20 individuals with spinocerebellar ataxia were randomly assigned to either four weeks of aerobic training or control group. Training was limited to 15 minutes of cycling for three days a week with no specifications regarding the intensity of cycling. The control group consisted of verbal health education and upper extremity stretching exercises in the seated position. Results demonstrated only slight improvements in ataxia severity with no changes in gait speed and balance with training.⁷

In the second study, eight individuals with spinocerebellar ataxia performed gait training using partial body weight support and a treadmill. Training consisted of 16 supervised sessions of 50 minutes over eight weeks. Results indicated that the training improved gait performance and cardiovascular fitness, but not ataxia severity.⁸

Our study will expand upon the prior studies by examining the effects of a structured, intensive aerobic training program. Aerobic exercise in degenerative cerebellar disease is worth investigation for the following reasons: (1) It may slow disease progression and improve ataxia severity as studies on ataxic animals demonstrate that aerobic training increases lifespan, motor function, and cerebellar Purkinje cell survival.^{9,10} (2) It will increase overall fitness as poor physical conditioning in individuals with cerebellar degeneration is associated with lower overall function and quality of life.¹¹ (3) We suspected that the slight improvements seen in prior human studies was due to the limited aerobic training performed.^{7,8}

In this study, we aim to (1) examine the extent to which people with cerebellar degeneration can perform rigorous aerobic exercise over a four-week intervention and (2) explore the intervention's effect on clinical outcomes. We chose outcome measures for ataxia severity, balance, and gait as these are the parameters most impacted by individuals with cerebellar degeneration.¹¹

Methods

This study ran from November 2018 to May 2019. It was conducted in accordance with the Declaration of Helsinki. All participants gave informed consent according to the human studies guidelines of the Columbia University Institutional Review Board, reference number AAAR5381. The study is registered at www.clinicaltrials.gov, number NCT03745248. The department of physical medicine and rehabilitation at Columbia Medical Center funded the study.

This was a technical (can individuals with degenerative cerebellar disease perform rigorous aerobic exercise) and operational (adherence, drop-out, adverse events, assessments completed) feasibility study. It used a single-blinded, randomized control design, with a non-training control group. The control group was allowed to participate in training after four weeks, but these data were not included for this study.

Individuals with degenerative cerebellar disease were assessed for eligibility to participate in the study by a member of the research team and recruited from the ataxia clinic at the Neurological Institute at New York Presbyterian-Columbia. Inclusion criteria for the study comprised cerebellar atrophy on magnetic resonance imaging, prevalence of ataxia on clinical exam, and the Scale for the Assessment and Rating of Ataxia¹² sitting subscore 0 (able to sit safely and ride stationary exercise bike). Participants were excluded if they had other neurological diseases, cognitive impairment (i.e. Mini-Mental State exam¹³ score <22), heart disease, joint pain, inability to exercise, the Scale for the Assessment and Rating of Ataxia walking subscore >6 (inability to walk without assistance), or if they were medically unstable. Results of genetic testing were obtained when available. Individuals with different types of cerebellar degeneration, including idiopathic and Multiple System Atrophy-Cerebellar type, were allowed to participate in the study as long as their predominant neurological deficit was ataxia. Clinically, all participants had evidence of at least mild ataxia (Scale for the Assessment and Rating of Ataxia score >3)¹⁴ for more than three months.

Participants were randomly assigned to aerobic training or no training. A stratified randomization, with a 1:1 allocation ratio and varying blocks, was used to assign treatment. The stratum variable was disease severity (mild (Scale for the Assessment and Rating of Ataxia score <10) and moderate (Scale for the Assessment and Rating of Ataxia score ≥ 10)).¹⁵ Participants in the aerobic group performed four weeks of cycling at home after one baseline assessment. A post-training assessment was performed at the completion of the four weeks. Individuals in the control group underwent two assessments, four weeks apart with no intervention. Control group participants were told to maintain their usual lifestyle and physical activity habits. After four weeks, control participants were allowed to enter an exercise program, but these data were excluded from analysis.

Group allocation was done after baseline assessment to ensure blinding. At the second assessment point, assessors (N.L. for clinical assessments and D.M. and I.O. for laboratory assessments) were blinded to group allocation, and participants were reminded not to reveal their allocation. Due to the nature of the intervention, none of the participants were blinded to assignment.

Assessments

The primary feasibility outcomes were as follows: (1) the extent to which participants adhered to the rigorous training program's frequency, duration, and intensity; (2) drop-out rates; and (3) adverse events. Adherence to frequency was calculated as the number of training sessions performed divided by 20 (number of sessions participants were expected to perform). Adherence to duration was met if participants' average training times were greater than 30 minutes. Adherence to intensity was met if participants' average heart rates during training were greater or equal to 72.5% (average of 65%, 70%, 75%, and 80%) of their maximum heart rate during cardiopulmonary exercise testing. Drop-out rate was calculated by dividing the number of participants who left the study by the total number of participants. Frequency of adverse events was calculated by the number of adverse events divided by total number of training sessions performed.

The primary clinical outcome measure was the Scale for the Assessment and Rating of Ataxia, a 40-point scale that has been validated in evaluating ataxia severity, which is the most important outcome measure for people with degenerative cerebellar disease.¹⁴ A score of zero indicates no signs of ataxia, whereas a score of 40 indicates the most severe ataxia. This scale has been shown to have excellent test-retest reliability, inter-rater reliability, and internal consistency.¹² The minimal clinically important difference is not clearly defined, but other clinical trials have used a reduction of 1.0 points on this scale as clinically meaningful.¹⁶

Cardiopulmonary exercise testing was used to determine maximal oxygen consumption to evaluate the effectiveness of training. It was measured by a breath-by-breath measurement of oxygen consumption with a Vmax Encore Metabolic System (CareFusion Corp, San Diego, CA, USA), while participants performed progressive ramped exercise test using an electronic-braked lower body cycle ergometer (CareFusion Corp, San Diego, CA, USA). After a three-minute warm-up at minimal resistance, the initial workload and individualized

ramping protocol were determined based on participant's weight, level of function, and current exercise profile. The individual then cycled at 60–65 revolutions per minute until achieving one of the following maximal oxygen consumption criteria: respiratory exchange ratio 1.1, increases in ventilation without concomitant increases in oxygen consumption, and/or maximum age-predicted heart rate. The test was also terminated if the cycling cadence dropped below 40 r/min for 5 seconds, or when the participant reached volitional exhaustion.¹⁷ A licensed medical physician (S.B.) was available during all cardiopulmonary exercise tests to monitor cardiac response.

Secondary outcome measures for gait and balance were also examined due to their clinical importance for individuals with degenerative cerebellar disease and being measured in other rehabilitative studies in this population.^{2–6} 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 Dynamic Gait Index¹⁸ and Timed Up and Go¹⁹ tests were performed according to established protocols.

For instrumental assessments, participants were equipped with reflective markers for the collection of kinematic data. Static standing balance was assessed by measuring postural sway on a split-belt treadmill instrumented with three-dimensional force plates under each belt (Bertec Instrumented Treadmill, Columbus, OH, USA). Participants stood on the treadmill for 60 seconds with hand at their sides with feet shoulder-width apart under two conditions: eyes open and eyes closed. Postural sway was determined as the distance traveled by the center of pressure in the middle 30 seconds of each trial. The Romberg Quotient was assessed by calculating the ratio between the sway path obtained with eyes opened and eyes closed.

After static standing, participants walked for 5 minutes at a constant predetermined speed. The trajectories of 48 reflective markers were collected at 200 Hz using a 10-camera motion capture system (Vicon Bonita-10 series, Oxford, UK). The farthest anterior position of the heel marker relative to the sacrum marker was used to define the heel strikes event.²⁰ Step length and step width were calculated as the longitudinal/perpendicular distance between the line connecting the right and left foot heel points at right heel strike. Step time was estimated as the time period between left and right heel strike. Maximum toe clearance was estimated as the highest point of the toe during the swing phase. Dynamic stability was quantified using the concept of margin of stability.²¹ The margin of stability in the antero-posterior and medio-lateral directions were calculated at right heel strike as the distance in the antero-posterior/medio-lateral direction between the forward/lateral edges of the base of support (toe marker/fifth metatarsal head of the leading leg) and the extrapolated center of mass. Outcome measures were calculated as the average values obtained during the last 40 right heel strikes of walking to ensure accurate data for analysis.²²

Intervention

The aerobic training consisted of four weeks of stationary bicycle training, five times a week. This amount of exercise was chosen as it correlated with the amount of exercise performed in balance training studies where positive results were depicted.^{2–6} If participants

did not have access to a stationary bike with a heart rate monitor, they were provided a ProGear 225 Folding Magnetic Upright Exercise Bike with Heart Pulse (Beverly Hills, CA). The exercise intensity prescription was based on the participant's maximal heart rate during cardiopulmonary exercise testing. During week 1, participants were asked to maintain 65% of the cardiopulmonary exercise testing (CPET) maximal heart rate for 30 minutes after a 5-minute warm-up. Exercise intensity increased by 5% every week until participants were able to maintain 80% of CPET maximal heart rate for 30 minutes. In addition, rate of perceived exertion (Borg scale)²³ was assessed on each training session with scores expected around 12 during initial training and 15 by the end of four weeks. At the end of the fourth week program, participants were told that they were no longer required to perform the training as part of the study but were encouraged to continue exercising with instructions.

An exercise log was provided for entering dates and duration of exercise. In addition, 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. Weekly phone calls were performed to answer questions, allow for the report of any adverse events, and encourage participants to continue exercise.

Statistical analysis

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

All analysis was done under intent-to-treat principles. The primary and secondary outcomes were analyzed using mixed effect model with group (two levels: aerobic training vs control) and time (two levels: pre vs post) and their interaction. Within-subject correlation was accounted by adding random intercept. For significant time by group interaction, the within-group changes were estimated using least squared mean.

As a proof of concept and feasibility study, multiple secondary outcomes were tested in this study to determine the most appropriate outcomes to test in a larger, Phase II trial. To account for this feature, multiple comparison correction was conducted to control the false discovery rate.²⁴

We used the results obtained in this feasibility study to determine effect sizes and standard deviations. Pass Software (v19.0.3) was then used to estimate sample size for future studies setting power to 0.8 and α at 0.05.

Results

Participant flow through the study is summarized in Figure 1, and baseline demographics of the aerobic training group and non-training group can be found in Table 1. There was no statistical difference in baseline characteristics between the two groups.

The diagnoses of the participants in the study included spinocerebellar ataxia ($n = 6$), idiopathic ataxia ($n = 7$), and Multiple System Atrophy, Cerebellar type ($n = 7$). The sex, age, duration of disease, and initial Scale for the Assessment and Rating of Ataxia score for each participant can be found in Supplemental Table 1.

All participants in the aerobic training group completed four weeks of training, and there was no drop-out. The training frequency, average heart rate, average training intensity, and average Borg Score for the aerobic training group is shown in Table 2. All of the participants in the aerobic training group completed four weeks of training. Eight out of 10 participants achieved the target of training at least five days per week. Nine of 10 participants achieved their target training heart rate (Table 2). The only reported adverse event from training was one case of mild back pain. The participant's back pain was relieved with medication, only occurred after one session, and did not hinder future aerobic training sessions.

Table 3 shows the baseline assessment results of the aerobic and control groups as well as assessments after four weeks of training for the aerobic group and four weeks of no training for the control group. Differences between the two assessments for each group were calculated and compared. There was a significant improvement in the Scale for the Assessment and Rating of Ataxia scores, walking speed, Timed Up and Go, maximal oxygen consumption, and Dynamic Gait Index scores after aerobic training with large effect sizes (0.655, 0.416, 0.344, 0.246, and 0.356, respectively) when compared to changes seen in the control group. Even with the small sample size, change in walking speed, maximal oxygen consumption, Dynamic Gait Index, and Timed Up and Go remained statistically significant after multiple testing correction (Table 3).

We estimate that a fully randomized controlled trial would only require seven participants per group for comparison of the Scale for the Assessment and Rating of Ataxia scores if the effect size seen in this feasibility trial is used. However, if the minimal clinically important difference of 1.0 points on the Scale for the Assessment and Rating of Ataxia is used instead, a sample size of 20 participants is required to have 80% power with α set at 0.05. A sample size of 23 participants was calculated for a study including the secondary outcomes of balance and gait.

Results for the static balance and gait analysis can be found in the [dummy_]Supplemental Materials (Supplemental Table 2 and 3). Although certain parameters showed significant positive changes with aerobic training (postural sway path Romberg Quotient, step length, maximum toe clearance, and margin of stability in anteroposterior direction), the results did not remain significant after correction for multiple comparisons. Nineteen participants per group would be required to have 80% power for comparison of gait parameters.

Discussion

Our findings suggest that intense aerobic training is feasible as an exercise modality in people with cerebellar degeneration. Nine of 10 participants achieved their target training heart rates. Eight out of 10 participants achieved the target of training at least five days per week with 30-minute training sessions. No serious adverse events were recorded. A

statistically significant improvement in ataxia severity, balance, fitness, and gait were seen with four weeks of aerobic training when compared to four weeks of no training in the control group. Static balance and gait parameters also showed improvement with aerobic training, but these measures did not remain significant after correction for multiple comparisons.

Prior to our study, there was little evidence regarding the effects of aerobic exercise on people with degenerative cerebellar disease. The previous two studies published indicated aerobic exercise had minimal benefits in cerebellar degeneration.^{7,8} We speculated, however, that the minimum improvements were due to participants performing inadequate aerobic exercise; for example, participants did not pedal long, hard, or fast enough to generate more robust benefits. It was unclear from previous studies whether intense aerobic exercise was a feasible treatment option for people with degenerative cerebellar disease.

Our study supports that intense aerobic exercise is acceptable to people with degenerative cerebellar disease. Adherence was high, with everybody exercising at least 30 minutes a day, three times per week. There was also no drop-out from the study. There are several possible factors explaining the high adherence and low drop-out rates: (1) there are no cures for this disease so individuals with cerebellar degeneration invested in the aerobic training, (2) the training was limited to only four weeks, and (3) the weekly phone call urging adherence was helpful. Overall, our data indicate that a larger clinical trial investigating the effects of aerobic training on degenerative cerebellar disease is feasible. It will be interesting to determine the effects of aerobic training over a longer duration, as adherence to the intense aerobic training will likely decrease.

Results of our study suggest possible benefits to people with degenerative cerebellar disease who perform a four-week aerobic exercise program. The average reduction in ataxia severity of 2.1 points seen with aerobic exercise in this pilot trial appears clinically meaningful if the minimal clinically important difference is taken to be 1.0 point on the Scale for the Assessment and Rating of Ataxia.¹⁶ With changes as low as 0.6 mL/kg/min found to be clinically meaningful, the average change in maximal oxygen consumption of 4.6 mL/kg/min also appears highly significant.²⁵ Although the improvements in the balance measures do not meet the criteria for clinical significance for other neurological diseases,²⁶ the improvements are similar to those seen in balance training studies.²⁻⁶ This is a surprising result in that aerobic exercise may be as beneficial for stability as a training program that focuses exclusively on balance. With other health benefits, including decreased risk of heart disease, diabetes, and stroke, the role of aerobic exercise in treatment of cerebellar degeneration should be explored further.

It is unclear the reason aerobic exercise appears to improve balance, gait, and ataxia severity. Most exercise requires a minimum of eight weeks to cause physiologic effects, so the benefits may not be a result of changes at the cellular level.²⁷ Thus, the benefits may be due to increased ability to compensate for deficits. For example, the cycling improved fitness which gave individuals longer ability to concentrate and to have less fatigue while doing tasks. Moreover, leg strengthening from the cycling may have improved stability. Future studies should examine whether training impacts disease progression.

One of the main limitations of this study is the small sample size. Another limitation is that the control group did not undergo any treatment. With the study's goal to determine the feasibility for individuals with cerebellar degeneration to partake in rigorous aerobic exercise and obtain sample size calculations for future studies, an active control group was not used. To control for both expectation and the effect of having attention, a future study should compare aerobic training to balance training or another activity such as tai chi, Pilates, or neuromuscular electrical stimulation. Another limitation of this study is that a heterogeneous group of degenerative cerebellar disorders was studied to ensure adequate enrollment. Thus, it is possible that aerobic training may be of more benefit in certain degenerative cerebellar disorders than others. With only a few individuals with each specific disease, this study is unable to answer this question. Finally, as the role of rigorous aerobic training in cerebellar degeneration has not been previously studied, a power analysis was not conducted prior to this study. Moreover, multiple secondary outcomes were included in the study to determine which factors should be examined in a larger phase II trial.

The main implication of this study is that intensive aerobic exercise appears to be acceptable to people with degenerative cerebellar disease, and a larger, more definitive trial investigating its role in degenerative cerebellar disease is feasible. We calculated that 23 individuals would be required in each group to have 80% power to detect changes in ataxia severity, balance, and gait. Although there was no drop-out in this study, we will conservatively estimate a 20% drop-out rate in a larger trial. Thus, 29 individuals would be required in a more definitive, future trial. In addition, future directions of study will be to examine longer term training effects of aerobic exercise and to compare this to an active control group such as balance training or tai chi. Aerobic training's impact on disease progression, which has been shown to occur in animal models, should also be explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical messages

- Intensive aerobic exercise is acceptable to individuals with DCD, and a trial studying its effects is feasible.
- Improvements in ataxia, balance, and gait in individuals with cerebellar degeneration who perform aerobic exercise are promising.

Figure 1.
CONSORT 2010 flow diagram.

Table 1.

Baseline characteristics of aerobic and control groups.

	Aerobic	Control	Total	P Value
Number of patients	10	10	20	
Age in years (SD)	53.8 (17.4)	46.1 (13.3)	50.0 (15.65)	0.28
SARA (SD)	9.1 (2.9)	10.35 (3.5)	9.6 (3.1)	0.40
Disease duration in years (SD)	5.5 (3.8)	5.3 (3.8)	5.4 (3.6)	0.91
Female/male	4/6	3/7	7/13	0.64
MSA-C/SCA/idiopathic	3/3/4	3/4/3	6/7/7	0.30

MSA-C, multiple system atrophy-cerebellar type; SCA, spinocerebellar atrophy; SD, standard deviation; SARA, Scale for the Assessment and Rating of Ataxia.

Table 2.

Aerobic training intensity.

ID	Training (days/week)	Average training heart rate	Average training intensity (percent of max CPET heart rate)	Average Borg score	Achieved target training rate
1	5	105	90%	14	Yes
4	3	120	88%	13	No
7	5	128	98%	13.5	Yes
8	5	138	82%	14	Yes
10	5	147	90%	15	Yes
12	5	97	70%	12	No
13	3	91	66%	14	No
14	6	94	84%	13	Yes
16	7	122	91%	14	Yes
18	6	124	77%	13	Yes

CPET, cardiopulmonary exercise testing.

Table 3.

Comparison of change between aerobic and control groups.

	Aerobic training			No training			Group difference comparisons	
	Baseline assessment ** (SD)	Post-training assessment (SD)	Difference (95% CI)	Baseline assessment (SD)	Assessment 2 (SD)	Difference (95% CI)	η^2	P value
SARA	9.1 (2.9)	7.0 (2.8)	-2.1 (-1.32, -2.88)	10.35 (3.5)	10.6 (3.5)	0.3 (0.03, 0.57)	0.655	<0.001
Walking speed (m/s)	0.99 (0.28)	1.14 (0.35)	0.15 (0.09, 0.21)	0.80 (0.35)	0.77 (0.35)	-0.03 (-0.03, -0.09)	0.416	0.002 *
TUG (seconds)	13.2 (8.0)	11.5 (7.4)	-1.7 (0.62, 2.78)	15.6 (7.3)	16.3 (8.8)	0.7 (-0.67, 2.07)	0.344	0.007 *
VO ₂ Max (mL/kg/ min)	23.4 (10.0)	28.1 (10.4)	4.6 (2.67, 6.59)	22.4 (5.6)	23.6 (6.9)	1.2 (-0.86, 3.06)	0.246	0.026 *
DGI	17.5 (3.5)	19.0 (3.3)	1.5 (0.76, 2.24)	14.5 (5.4)	14.3 (5.1)	-0.20 (-0.98, 0.58)	0.356	0.006 *

SD, standard deviation; CI, confidence interval; η^2 , effect size; SARA, Scale for the Assessment and Rating of Ataxia; TUG, Timed UP and Go test; VO₂Max, maximal oxygen consumption; DGI, dynamic gait index.

* Indicates remained significant after multiple comparison correction.

** When comparing baseline assessments between groups for all outcomes, there is no statistical difference ($P > 0.05$).