Original Article

CLINICAL REHABILITATION

Clinical Rehabilitation
1–14

DOI: 10.1177/0269215517736903
journals.sagepub.com/home/cre
SAGE

Can rehabilitation improve the health and well-being in Friedreich's ataxia: a randomized controlled trial?

Sarah C Milne[1,2,3], Louise A Corben[1,3,4], Melissa Roberts[2], Anna Murphy[5,6], Geneieve Tai[1], Nellie Georgiou-Karistianis[3], Eppie M Yiu[1,4,7] and Martin B Delatycki[1,3,4,8]

Abstract

Objective: To determine the effectiveness of a six-week rehabilitation programme followed by a home exercise programme for Friedreich's ataxia.

Design: Randomized, delayed-start control single-blind trial.

Setting: Outpatient rehabilitation centre.

Subjects: Ambulant or non-ambulant individuals with Friedreich's ataxia.

Intervention: Participants were randomized to a six-week outpatient rehabilitation programme, immediately (intervention group) or after a six-week delayed-start (control group). The rehabilitation was followed by a six-week home exercise programme.

Main measures: The primary outcome was the Functional Independence Measure. Other measures included the Friedreich Ataxia Impact Scale and the Friedreich Ataxia Rating Scale. Outcomes were administered at baseline, 6, 12 and 18 weeks.

Results: Of 159 individuals screened, 92 were excluded and 48 declined to participate. A total of 19 participants were enrolled in the study. There was no significant difference in Functional Independence Measure change from baseline to six weeks in the intervention group (mean ± standard deviation, 2.00 ± 3.16) as compared to the control group (0.56 ± 4.06). Change in the Friedreich Ataxia Impact Scale body movement subscale indicated a significant improvement in health and well-being in the intervention group compared to the control group ($P = 0.003$). Significant within-group improvements in the Friedreich

[1]Bruce Lefroy Centre, Murdoch Children's Research Institute, Parkville, VIC, Australia
[2]Physiotherapy Department, Monash Health, Clayton, VIC, Australia
[3]Monash Institute of Cognitive and Clinical Neurosciences and School of Psychological Sciences, Monash University, Melbourne, VIC, Australia
[4]Department of Paediatrics, The University of Melbourne, Melbourne, VIC, Australia
[5]Monash Ageing Research Centre, Monash University, Melbourne, VIC, Australia
[6]Clinical Research Centre for Movement Disorders and Gait, Monash Health, Cheltenham, VIC, Australia
[7]Department of Neurology, Royal Children's Hospital Melbourne, Parkville, VIC, Australia
[8]Victorian Clinical Genetics Services, Parkville, VIC, Australia

Corresponding author:
Professor Martin B Delatycki, Bruce Lefroy Centre, Murdoch Children's Research Institute, 50 Flemington Road, Parkville, VIC 3052, Australia.
Email: martin.delatycki@vcgs.org.au

Ataxia Impact Scale and the motor domain of the Functional Independence Measure post-rehabilitation were not sustained post-home exercise programme.
Conclusion: Our study indicates that rehabilitation can improve health and well-being in individuals with Friedreich's ataxia; however, a larger study is required to have sufficient power to detect a significant change in the most sensitive measure of function, the motor domain of the Functional Independence Measure.

Keywords
Friedreich's ataxia, spinocerebellar ataxias, gait, cerebellum, rehabilitation, activities of daily living

Date received: 11 July 2017; accepted: 22 September 2017

Introduction

Clinically, rehabilitation is the mainstay in alleviating the physical symptoms and mobility decline associated with Friedreich's ataxia.[1,2] However, inaccessibility to quality care, therapist inexperience and minimal scientific evidence limit its utilization.[3] A number of published studies have demonstrated positive outcomes following physical rehabilitation in ataxia.[4–7] These studies have shown changes in ataxia, balance and function, but suggest disorders with a component of afferent ataxia, such as Friedreich's ataxia, are not as amenable to rehabilitation.[5]

There are no definitive answers as to the best type and dosage of rehabilitation intervention for individuals with Friedreich's ataxia. Evidence for rehabilitation in degenerative ataxia is in its infancy, with only three small randomized controlled trials examining its effects.[7–9] However, emerging evidence suggests a multifaceted approach to rehabilitation may be most effective,[1] while whole-body coordination and static and dynamic balance exercises have the largest body of supportive evidence.[2]

Interestingly, other impairments that rehabilitation could target have not been a focus of interventional studies in Friedreich's ataxia. As muscle weakness is not considered a major contributor to mobility decline in Friedreich's ataxia,[10] resistance training has not been examined in this population. However, evidence in other degenerative populations suggests that strengthening is highly beneficial.[11,12] Furthermore, the myopathy and pyramidal weakness in Friedreich's ataxia may further compound movement difficulties related to ataxia.[13,14] Additionally, the absence of evidence does not correspond with clinical practice, where muscle strengthening and stretching are frequently prescribed.[3] This mismatch between current practice and the evidence may be related to clinicians' poor understanding of Friedreich's ataxia[3] or indicates the need for research in an area evaluated as clinically beneficial by clinicians.

The resulting proprioceptive and cutaneous sensory loss that differentiates Friedreich's ataxia from many of the other degenerative ataxias[15] has similarly not been well researched. Diminished afferent input is likely to impede rehabilitation as it poses additional challenges for motor relearning.[5,16] As a result, in other neurologically impaired populations, interventions aimed at enhancing proprioception, in conjunction with other rehabilitation approaches such as balance training, have increasingly been used.[17,18] These interventions have demonstrated improvements in postural control, motor function, ataxia and gait.[17,18] Techniques applied have included vibration, passive and active foot and ankle mobilization and somatosensory stimulation training.[17]

As a result of this varied evidence for possible rehabilitative interventions in Friedreich's ataxia, the aim of this randomized controlled trial was to examine the effects of a six-week multifaceted rehabilitation programme for individuals with Friedreich's ataxia compared to a delayed-start control. The rehabilitation in this study was drawn from both available evidence and clinical expertise, incorporating strengthening, balance training, functional mobility, mobilizing and stretching for proprioceptive stimulation, postural and coordinative control and cardiovascular fitness exercise.

The rehabilitation was individualized and targeted at specific impairments thought to contribute to functional decline.[19]

The secondary aim of this study was to evaluate the effect of a home exercise programme following the rehabilitation, as the prescription of a home exercise programme is standard practice in Australia.

Methods

This study is a single-blinded randomized controlled delayed-start trial comparing six weeks of rehabilitation followed by a six-week home exercise programme (intervention group) or no intervention for six weeks followed by six weeks of rehabilitation and a six-week home exercise programme (control group). This study was approved by the Monash Health Human Research Ethics Committee (HREC number 12134B). All participants (or their parents/guardians) provided written informed consent as per the Declaration of Helsinki. The study was registered prospectively with the Australian New Zealand Clinical Trials Registry (ACTRN12612000694819).

Recruitment and selection criteria

Between June 2015 and August 2016, individuals attending the Friedreich's ataxia Multidisciplinary Clinic at Monash Medical Centre, Melbourne, Australia, or on the specialized clinic database were screened for enrolment by the Friedreich Ataxia Multidisciplinary Clinic clinicians. Eligible individuals with Friedreich's ataxia were sent letters of interest regarding the study via email or mail.

Eligible participants had a diagnosis of Friedreich's ataxia with homozygosity for a GAA trinucleotide expansion in intron 1 of *FXN*;[20] a Friedreich Ataxia Rating Scale functional staging score[21] between 2 and 5 (2 = symptoms present, recognized by patient but still mild, 5 = confined but can navigate a wheelchair and can perform some activities of daily living that do not require standing or walking); aged at least 15 years; and who were deemed to have the potential to benefit from physiotherapy.

Participants were ineligible if they had an orthopaedic injury that limited their ability to mobilize or weight-bear, another illness that acutely reduced their functional capacity, were pregnant or had received major orthopaedic surgery or botulinum toxin injections in the last six months. Regular long-standing botulinum toxin paraspinal injections were removed from exclusion criteria after trial commencement as their effects were not considered to impact function and thus unlikely to impact outcomes.

Registration and random allocation

Participants were enrolled by the chief investigator. Each participant was assigned a de-identified study number which was emailed to an independent statistician for randomization. Participants were allocated 1:1 to either the intervention group or the control group using a computer-generated randomization list. The randomization plan included blocking (block size = 2) to ensure balance between groups. As the block size was two, only even numbers of participants were randomized by the study statistician (except for the last round of recruitment) in order to prevent allocation bias. The independent statistician emailed the allocation back to the chief investigator. Randomization and allocation occurred prior to the baseline assessment to provide time for participants to arrange work/life commitments for the duration of the six-week outpatient rehabilitation programme. Examples of this included arranging annual or planned personal leave, changing the days of support by carers and organizing transport with family members.

Intervention

The intervention was conducted at the Kingston Centre, Melbourne, Australia, between August 2015 and December 2016. The intervention was an individualized outpatient rehabilitation programme aimed at improving function. The programme was conducted by a physical therapist and consisted of 2–3 hours of physiotherapy, supervised gym exercises and aquatic physiotherapy, three times per week.

Therapy was classified into seven 'rehabilitation domains': strengthening, postural control, coordination and control, functional mobility, balance training, stretching and mobilizing, and cardiovascular fitness. The domains received ratification from three experienced clinical physical therapists specializing in the management of Friedreich's ataxia. The following approaches were undertaken for each of the domains:

1. Strengthening was performed in standing, sitting or lying and focused on lower limb or trunk muscles. Upper limb muscles were strengthened if there was a postural control component to the exercise. Rubber resistant bands; gym equipment; anti-gravity strengthening, such as calf raises; facilitated movement; and turbulence and buoyancy in the hydrotherapy pool were options used for strengthening. Participants performed 2–3 sets[11] of 8–10 repetitions; intensity was set at a level to ensure correct movement patterns and appropriate eccentric control.
2. Postural control involved facilitated or independent performance of selective pelvic, trunk and scapular movements, as well as rotational control in the hydrotherapy pool.
3. Coordination and control focused primarily on eccentric movements and physical therapist-facilitated movements of the lower limb.
4. Functional mobility incorporated practice and part-practice of functional movements, such as walking, stairs and lying to sitting. The hydrotherapy pool was utilized to practice dynamic walking, such as turning and stopping.
5. Balance training was completed on land and in the hydrotherapy pool and involved both dynamic and static standing and sitting balance.
6. Stretching was performed to lengthen muscles for optimal positioning during functional mobility. Mobilizing focused on the foot and ankle in order to provide sensory stimulation to enhance proprioception.[17] See Online Appendix A for options for foot and ankle mobilizing and stretching exercises.
7. Cardiovascular fitness exercises included stationary cycling, swimming, arm ergonometer and standing endurance as appropriate for each participant.

To provide an individualized rehabilitation programme, the physical therapist assessed each participant's function and impairments and clarified goals. Each exercise or treatment was specific to each participant; however, it was required to sit within a domain. Exercises were progressed according to the individual's progression in the performance of each exercise, their fatigue and motivation levels, and their goals.

Participants in the control group received the intervention after a six-week delay. Immediately following the rehabilitation, an individualized home exercise programme was given to all participants. The home exercise programme included aquatic, home-based and/or gym exercises, based on the participant's preference. Participants were asked to document the exercises completed in an exercise diary.

Data collection, assessor blinding and outcome measures

The following outcomes were measured:

1. The primary outcome was the Functional Independence Measure which evaluates a person's ability to perform activities of daily living. It has a maximum score of 126 (complete independence) and a minimum of 18 (complete dependence).[22] The total Functional Independence Measure and motor domain of the Functional Independence Measure[22] scores were analysed.
2. Friedreich Ataxia Impact Scale[23] measured participant health and well-being. A greater percentage indicates reduced health and well-being in eight independent subscale scores.[24]
3. Patient Global Impression of Change measured perceived benefit from rehabilitation.[25] The 7-point Likert scale ranges between 0 and 7 (0 = No change, 7 = A great deal better, and a considerable improvement that has made all the difference).

4. Goal Attainment Scale[26] was used to record achievement and level of difficulty of three participant-specified goals.
5. The Friedreich Ataxia Rating Scale[21] measured disease severity (maximum deficit = 126).
6. Berg Balance Scale[27] measured static and dynamic balance. It has a highest possible score of 56 indicating excellent balance and a lowest score of zero.[27]
7. Modified Tardieu Scale[28] was used to measure gastrocnemius and soleus spasticity and muscle length.
8. Foot Posture Index[29] evaluated foot posture with zero indicating a neutral foot, and scores of 12 and −12 indicating severe pronation and supination, respectively.
9. GAITRite® instrumented walkway recorded spatiotemporal gait parameters at preferred speed.
10. Phone-FITT[30] assessed changes in physical activity performed outside the trial.

Outcome measures were administered at baseline and six weeks after the control or intervention period (six-week visit). To further evaluate the impact of the rehabilitation and the home exercise programme, the outcomes were also measured immediately after the delayed-start rehabilitation for the control group (12 weeks after baseline) and immediately after the home exercise programme (12 weeks after baseline for the intervention group and 18 weeks after baseline for the control group).

A physical therapist blinded to group allocation completed the outcome assessments. The physical therapist was a Functional Independence Measure–certified assessor. Functional Independence Measure scores were attained through structured interview with the participant.[31]

Clinical characteristics measured at baseline were age at disease onset, disease duration, age and the genetic mutations related to Friedreich's ataxia: the smaller *FXN* GAA repeat size and the larger *FXN* GAA repeat size.[20] Adverse events were also recorded.

Data analysis

This study involved two components: (1) between-group analysis to determine rehabilitation effectiveness and (2) within-group analysis collating data from all participants to measure home exercise programme effectiveness. Due to the small sample size, rehabilitation effectiveness was analysed utilizing independent sample *t*-tests to compare the change from baseline and the six-week visit between groups, in each of the continuous variables. Berg Balance Scale scores were analysed separately for non-ambulant and ambulant participants to account for skewness of data. Patient Global Impression of Change scores were dichotomized with the cut-off score for clinically meaningful change set at 5 (moderately better, and a slight but noticeable change). A Fisher's exact test was utilized to test the differences between groups. The primary intervention effect on the primary outcome, Functional Independence Measure, was estimated along with 95% confidence interval (CI) levels. A 3.00-point threshold for clinical relevance was set on the Functional Independence Measure.

To ascertain the effects of the home exercise programme, a secondary analysis was conducted pooling data from both groups. According to normality of distribution, paired *t*-test or Wilcoxon signed rank tests were utilized to determine change in pre-rehabilitation and immediately after the rehabilitation (post-rehabilitation); and pre-rehabilitation and immediately after the home exercise programme (post-home exercise programme). Linear regression was utilized to predict if any clinical parameters, or number of rehabilitation or home exercise programme sessions completed influenced performance on outcome measures. Significance was recorded as $P < 0.05$. Analysis was performed using STATA (StataCorp, 2015, Stata Statistical Software: Release 14; College Station, TX: StataCorp LP).

A power analysis was conducted using data from an earlier study investigating the effect of inpatient rehabilitation.[6] This study found a significant Functional Independence Measure score change coefficient of 11.43 (SD = 7.92) in individuals with Friedreich's ataxia after rehabilitation.[6] Compared with an estimated 0.00-point change with no intervention and accounting for dropout, we required a sample size of 16 people per group (power = 0.90, $\alpha = 0.05$).

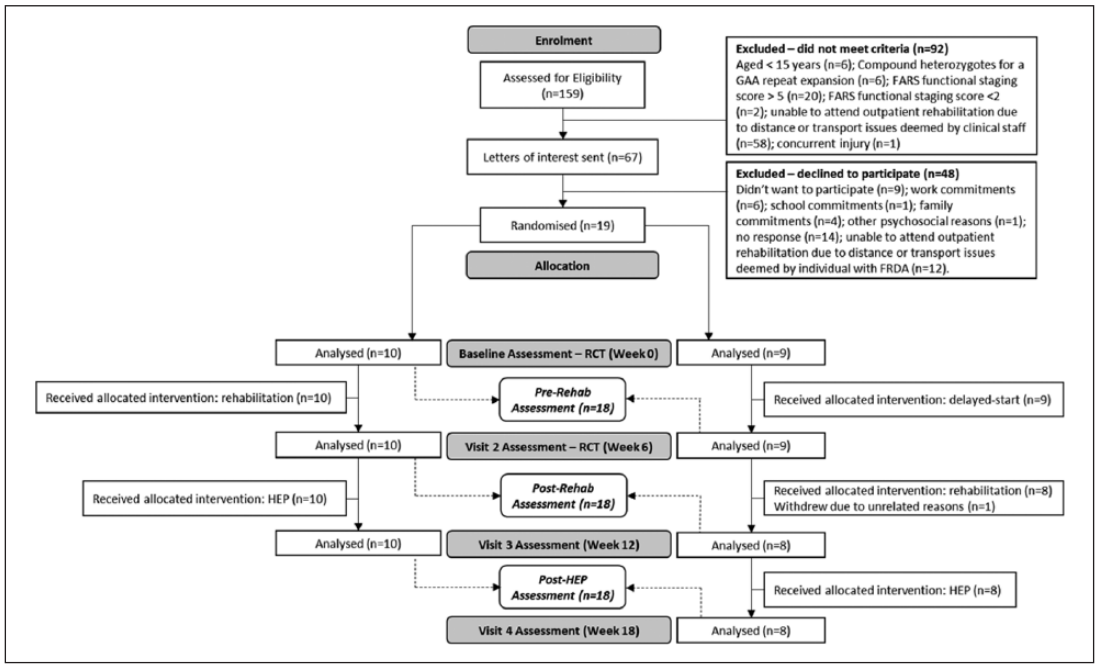

Figure 1. Study flow diagram.
FRDA: Friedreich's ataxia; RCT: randomized controlled trial; Rehab: rehabilitation; HEP: home exercise programme.

Results

A total of 159 individuals with Friedreich's ataxia were screened for eligibility. Of these individuals, 140 were excluded. As a result, 19 participants were enrolled in the study. Nine participants were randomized to the control group and 10 to the intervention group. Between baseline and the six-week visit, all 19 participants received their allocated intervention; therefore, an intention-to-treat analysis was not required. One control participant withdrew after completing the six-week visit, for reasons unrelated to the study; therefore, their data were excluded from the pooled data analysis. See Figure 1 for study flow.

Clinical and demographic details of the participants at baseline are displayed in Table 1. There were no significant differences between the groups at baseline. Seven participants completed the gait analysis assessment, one did not have adequate walking endurance and the remaining participants were non-ambulant.

There was no significant difference in the Functional Independence Measure, between the groups from baseline to six-week visit (Table 2). The clinical relevant threshold of 3.0 points on the Functional Independence Measure sat within the 95% CI for within-group difference. There was no significant between-group difference in the Functional Independence Measure motor domain. However, there was a significant within-group increase for the intervention group while the control group remained unchanged from baseline to the six-week visit. The control group was not influenced by a change in physical activity as indicated by the Phone-FITT.

There was a significant between-group difference in the Friedreich Ataxia Impact Scale body movement subscale change between baseline and the six-week visit (Table 2). Fisher's exact test identified a significant between-group difference in the Patient Global Impression of Change scores at the six-week visit, with 80% ($n = 8$) in the intervention and 11% ($n = 1$) in the control group indicating a clinically meaningful change ($P = 0.005$).

At the six-week visit, 8 out of 30 Goal Attainment Scale goals were achieved in the

Table 1. Demographics and clinical parameters at baseline.

	Control group (n = 9)	Intervention group (n = 10)	Significance between groups
Age, years	35.94 ± 15.11	37.73 ± 9.81	P = 0.761
Gender (male:female)	6:3	2:8	P = 0.055
Age of onset, years	15.00 ± 7.63	14.60 ± 9.79	P = 0.923
GAA1 repeat size	635.67 ± 144.19	586.80 ± 229.84	P = 0.591
GAA2 repeat size	922.11 ± 119.40	912.90 ± 150.99	P = 0.885
Disease duration, years	20.93 ± 14.36	23.12 ± 8.84	P = 0.691
Friedreich Ataxia Rating Scale total	90.50 ± 21.04	101.30 ± 22.49	P = 0.296
Functional Independence Measure	102.00 ± 14.65	97.60 ± 17.91	P = 0.568
Ambulation status (ambulant:non-ambulant)	5:4	3:7	P = 0.255

GAA1: GAA repeat size of the smaller FXN allele; GAA2: GAA repeat size of the larger FXN allele.
Data are expressed as mean ± SD or ratio.

intervention group, whilst 2 out of 27 goals in the control group were achieved. Of the goals achieved, one was rated as extreme, eight moderate and one as minor difficulty to achieve. There were no significant differences in the Modified Tardieu Scale, Foot Posture Index or spatiotemporal gait variables, except for a between-group difference in base of support change (mean difference: 1.65 cm, 95% CI: 0.69 to 2.62, $P = 0.007$).

Three participant-reported adverse events occurred between baseline and the six-week visit in the intervention group, while six were reported in the control group. Adverse events in the intervention group included hip pain, knee pain and fatigue. Falls, hip and knee pain, a viral infection and burns from a domestic chemical (unrelated to study participation) were reported by the control group.

The pooled data identified significant within-group improvements in the Functional Independence Measure motor domain and Friedreich Ataxia Impact Scale subscales post-rehabilitation, which were not sustained after the home exercise programme (Table 3). However, post-home exercise programme, the Berg Balance Scale for non-ambulant participants and the Friedreich Ataxia Rating Scale both indicated significant improvements compared with pre-rehabilitation scores (Table 3). In total, 61% (11/18) of participants still indicated a Patient Global Impression of Change score reflecting maintenance of clinically meaningful change after the home exercise programme.

On average, the time allocated to each rehabilitation domain per week was 2 hours on strengthening, 1.5 hours on postural control, 1 hour and 10 minutes on functional mobility, 50 minutes on balance training, 40 minutes on coordination and control, 16 minutes on stretching and mobilizing and 8 minutes on cardiovascular fitness. See Online Appendix B for an example weekly programme for an ambulant participant and a non-ambulant participant.

Participants missed a mean of 2.41 ± 3.26 days of rehabilitation. The main reasons were transport issues, intercurrent illness and fatigue. The number of sessions missed had no influence on rehabilitation outcomes (data not shown). Participants completed their home exercise programme on an average of 22.06 ±12.10 days in total, ranging from 0 to 153 minutes per week. See Online Appendix C for the average allocation and main exercises performed in the home exercise programme. Total number of days the home exercise programme was performed, but not average time spent on the home exercise programme, predicted improvement in Functional Independence Measure motor domain after the home exercise programme ($F(1,16) = 9.80$, $P < 0.007$, $R^2 = 0.38$).

To measure the influence of clinical parameters and baseline function on the outcomes post-rehabilitation, two outliers were identified and removed from the analysis. These participants had changes in Functional Independence Measure motor domain of

Table 2. Outcomes at baseline and the six-week visit, within-group and between-group comparisons.

Outcome measures	Group	Baseline score	Six-week visit score	Change score baseline to six weeks	Within-group significance (with 95% confidence intervals)	Between-group significance (with 95% confidence intervals)
Functional Independence Measure	Intervention	97.60 (17.91)	99.60 (15.59)	2.00 (3.16)	$t(9) = 2.00$ (−0.26 to 4.26), $P = 0.077$	$t(17) = 0.87$ (−4.95 to 2.06), $P = 0.397$
	Control	102.00 (14.65)	102.56 (13.26)	0.56 (4.06)	$t(8) = 0.41$ (−2.57 to 3.68), $P = 0.693$	
Functional Independence Measure – Motor Domain	Intervention	64.70 (17.39)	67.20 (15.08)	2.50 (3.27)	$t(9) = 2.41$ (0.16 to 4.84), $P = 0.039$[a]	$t(17) = 1.52$ (−5.96 to 0.96), $P = 0.146$
	Control	68.11 (13.97)	68.11 (12.72)	0.00 (3.87)	$t(8) = 0.00$ (−2.98 to 2.98), $P = 1.000$	
Friedreich Ataxia Rating Scale	Intervention	101.30 (22.49)	101.05 (23.94)	−0.25 (5.15)	$t(9) = -0.13$ (−3.93 to 3.43), $P = 0.881$	$t(17) = -0.40$ (−3.86 to 5.70), $P = 0.691$
	Control	90.50 (21.04)	91.17 (21.15)	0.67 (4.67)	$t(8) = 0.428$ (−2.92 to 4.26), $P = 0.680$	
Friedreich Ataxia Impact Scale – Movement Subscale	Intervention	31.84 (22.74)	19.62 (15.12)	−12.24 (10.51)	$t(9) = -3.86$ (−19.75 to 4.72), $P = 0.005$[a]	$t(17) = -3.40$ (5.97 to 25.52), $P = 0.003$[b]
	Control	33.48 (14.67)	36.99 (21.26)	3.51 (9.58)	$t(8) = 1.10$ (−3.85 to 10.87), $P = 0.304$	
Friedreich Ataxia Impact Scale – ADL Subscale	Intervention	52.03 (24.39)	42.03 (18.66)	−10.00 (19.89)	$t(9) = -1.59$ (−24.23 to 4.23), $P = 0.146$	$t(17) = -0.01$ (−17.90 to 17.70), $P = 0.990$
	Control	51.39 (27.91)	41.28 (30.76)	−10.10 (16.47)	$t(8) = -1.84$ (−22.77 to 2.56), $P = 0.103$	
Friedreich Ataxia Impact Scale – Lower Limb Subscale[c]	Intervention	62.62 (29.72)	47.38 (36.27)	−15.24 (13.40)	$t(4) = -2.54$ (−31.88 to 1.40), $P = 0.064$	$t(8) = -0.52$ (−41.42 to 26.18), $P = 0.617$
	Control	80.95 (13.49)	58.10 (35.41)	−22.86 (29.91)	$t(4) = -1.71$ (−59.99 to 14.30), $P = 0.163$	
Friedreich Ataxia Impact Scale – Upper Limb Subscale	Intervention	29.84 (18.81)	25.47 (18.34)	−4.38 (8.83)	$t(9) = -1.57$ (−8.67 to 9.71), $P = 0.152$	$t(17) = -1.02$ (−5.20 to 15.00), $P = 0.321$
	Control	27.08 (28.63)	27.60 (28.39)	0.52 (11.95)	$t(8) = 0.13$ (−10.69 to 1.94), $P = 0.899$	

ADL: activities of daily living.
Data represented as mean (SD).
[a]Statistically significant within group.
[b]Statistically significant between groups.
[c]Only ambulant participants are directed to complete this subscale.

Table 3. Mean scores at pre-rehabilitation, post-rehabilitation and post-home exercise programme for all participants.

Variable	Mean score[a]			Within-group difference (with 95% confidence intervals)	
	Pre-rehab	Post-rehab	Post-HEP	Baseline vs. post-rehab[b]	Baseline vs. post-HEP[c]
FIM Score	99.83 ± 16.10	101.94 ± 14.87	99.89 ± 16.00	$t(17) = 1.93$ (−0.20 to 4.42), $P = 0.071$	$t(17) = 0.05$ (−2.22 to 2.33), $P = 0.960$
FIM Motor Domain Score	66.28 ± 15.48	68.72 ± 14.31	67.00 ± 15.24	$t(17) = 2.36$ (0.26 to 4.63), $P = 0.031$[d]	$t(17) = 0.83$ (−1.11 to 2.56), $P = 0.418$
FARS Score	97.28 ± 22.24	96.42 ± 22.82	94.03 ± 23.21	$t(17) = -0.92$ (−2.84 to 1.12), $P = 0.372$	$t(17) = -2.66$ (−5.83 to −0.67), $P = 0.017$[d]
Friedreich Ataxia Impact Scale					
Body Movement Subscale	35.16 ± 21.87	27.70 ± 19.67	29.92 ± 23.17	$t(17) = -2.93$ (−12.82 to −2.09), $P = 0.009$[d]	$t(17) = -1.35$ (−13.29 to 2.91), $P = 0.194$
ADL Subscale	48.44 ± 27.33	40.89 ± 23.98	42.29 ± 24.18	$t(17) = -2.05$ (−15.31 to 0.21), $P = 0.056$	$t(17) = -1.71$ (−13.71 to 1.41), $P = 0.105$
Lower Limb Subscale[e]	65.21 ± 28.46	48.54 ± 31.47	54.10 ± 29.19	$t(8) = -2.57$ (−31.62 to −1.71), $P = 0.033$[d]	$t(8) = -1.79$ (−25.41 to 3.19), $P = 0.111$
Upper Limb Subscale	29.34 ± 23.71	25.17 ± 20.39	29.17 ± 22.43	$t(17) = -2.18$ (−8.20 to −0.13), $P = 0.044$[d]	$t(17) = -0.08$ (−4.77 to 4.42), $P = 0.9374$
Berg Balance Scale					
Ambulant participants	28.00 ± 11.89	31.29 ± 11.87	30.71 ± 13.87	$t(6) = 2.04$ (−0.66 to 7.24), $P = 0.088$	$t(6) = 1.56$ (−1.55 to 6.98), $P = 0.170$
Non-ambulant participants	1.00 (10)	2.00 (10)	1.00 (12)	$z = 2.07$, P=0.039[d]	$z = 2.22$, $P = 0.026$[d]

(Continued)

Table 3. (Continued)

Variable	Mean score[a]			Within-group difference (with 95% confidence intervals)	
	Pre-rehab	Post-rehab	Post-HEP	Baseline vs. post-rehab[b]	Baseline vs. post-HEP[c]
GAITRite® parameters					
Velocity (cm/s)	73.82 ± 25.50	77.15 ± 25.05	69.69 ± 22.78	$t(6) = 0.63$ (−9.63 to 16.29), $P = 0.552$	$t(6) = -0.84$ (−16.16 to 7.90), $P = 0.433$
Stride length (cm)	105.24 ± 22.66	109.80±21.67	105.67 ± 21.73	$t(6) = 1.02$ (−6.42 to 15.55), $P = 0.349$	$t(6) = 0.11$ (−9.68 to 10.55), $P = 0.920$
Base of support (cm)	13.53 ± 6.84	14.81 ± 7.16	13.12 ± 7.55	$t(6) = 1.09$ (−1.61 to 4.18), $P = 0.319$	$t(6) = -0.39$ (−3.02 to 2.20), $P = 0.714$
Swing %[f]	34.23 ± 4.22	34.75 ± 3.94	33.64 ± 4.15	$t(6) = 0.78$ (−1.12 to 2.16), $P = 0.466$	$t(6) = -0.63$ (−2.90 to 1.72), $P = 0.555$
Double support %[f]	31.92 ± 8.42	31.18 ± 8.24	34.43 ± 10.66	$t(6) = -0.57$ (−3.92 to 2.44), $P = 0.591$	$t(6) = 0.83$ (−4.89 to 9.91), $P = 0.439$
Stride length variability (cm)	7.57 ± 2.04	7.64 ± 3.31	8.63 ± 3.37	$t(6) = 0.05$ (−2.68 to 2.80), $P = 0.958$	$t(6) = 1.64$ (−0.52 to 2.63), $P = 0.153$
Base of support variability (cm)	3.92 ± 1.42	4.25 ± 1.54	4.18 ± 1.40	$t(6) = 1.00$ (−0.47 to 1.12), $P = 0.354$	$t(6) = 0.83$ (−0.50 to 1.02), $P = 0.437$
Step time variability (s)	0.05 (0.13)	0.06 (0.15)	0.11 (0.13)	$z = 0.68$, $P = 0.497$	$z = 1.35$, $P = 0.176$

IQR: interquartile range; FIM: Functional Independence Measure; FARS: Friedreich Ataxia Rating Scale; ADL: activities of daily living; HEP: home exercise programme; Rehab: rehabilitation.
[a]Data represented as mean ± standard deviation or median (IQR) if non-parametric data.
[b]Paired sample *t*-tests or Wilcoxon signed rank test *P* values between baseline and post-rehabilitation scores.
[c]Paired sample t-tests or Wilcoxon signed rank test *P* values between baseline and post-home exercise scores.
[d]Significant difference between scores.
[e]Only ambulant participants are directed to complete this subscale.
[f]Percentage of the gait cycle.

13 and 7 post-rehabilitation which corresponded to Patient Global Impression of Change scores indicating no change. A lower Functional Independence Measure motor domain at baseline (worse function) predicted greater improvement post-rehabilitation ($F(1,14) = 10.37$, $P = 0.006$, $R^2 = 0.43$). None of the clinical parameters or Friedreich Ataxia Rating Scale score had a significant influence on rehabilitation outcomes.

Discussion

Although a pool of 159 potentially eligible individuals were identified through a specialized Friedreich's ataxia multidisciplinary clinic, after screening 92 did not meet inclusion criteria and a further 48 declined to participate. The primary barriers to participation included effort and cost of travelling to the rehabilitation facility, and work and family commitments. Consequently, the required sample size was not recruited, and the study was inadequately powered. Nonetheless, the findings provide evidence to suggest rehabilitation can improve the health and well-being, motor function and balance in individuals with Friedreich's ataxia. Moreover, the absence of any major adverse event and no report of worsening in physical function after rehabilitation indicate the safety of this intervention.

This study is the first to report improvements in function after short-term outpatient rehabilitation in a cohort of individuals with Friedreich's ataxia. Two studies have previously examined long-term rehabilitation (one in conjunction with Achilles lengthening surgery[32]) of five years[7] and seven to eight months[32] duration, in individuals with Friedreich's ataxia. Both studies identified significant effects on function;[7,32] however, neither study commented on the feasibility and implications for the individual's daily life. This study chose six weeks of outpatient therapy as rehabilitation appears to provide functional improvement in individuals with degenerative ataxia after four weeks,[8] although greater improvements are seen with longer durations.[6,7,32] The six-week timeframe also considered the impact on work, school and family commitments; for both participants in the study, and general feasibility of the intervention.

Participants were asked to continue the programme at home to extend or sustain improvements; however, frequency of exercise performance was highly variable and results were not sustained. This was consistent with a study by Ilg and colleagues,[5] where individuals with a component of afferent ataxia did not retain improvements in balance and ataxia improvements after four weeks of intensive coordinative training.[5] The variable levels of home exercise completion in both studies reflect challenges seen in clinical practice[3] and highlight the requirement for further work in the development of effective home exercise programmes. A focus on minimizing the internal barriers[3] and providing the psychosocial benefits that appear critical to enhancing adherence, such as allowing choice, control and connection with the therapist,[33] is urgently required.

As a large part of the rehabilitation programme involved strengthening, the six-week duration may not have been long enough to provide maximal benefit. Moreover, as the intensity of strengthening exercises was reduced to ensure correct movement technique, and was not measured relative to one repetition max, the intensity may have been suboptimal for strength gains. Two systematic reviews evaluating strength training in Parkinson's disease and multiple sclerosis[11,12] found strength gains after three weeks of strength training; however, the majority of studies used training of greater than eight weeks duration. Strength training improved balance, gait and motor symptoms;[11,12] however, functional gains were less consistent in multiple sclerosis.[12] This potentially indicates the pathological mechanisms of weakness may influence the effects of strengthening.[11] In this trial, functional gains were seen but, due to the multifaceted nature of the intervention, it is impossible to directly attribute these gains to the strengthening component of the rehabilitation. Nor is it possible to ascertain if the intensity of resistance in the strength training component of this rehabilitation was adequate. Given the multifactorial cause of weakness in Friedreich's ataxia,[13,14,34] the ideal strengthening intensity and duration may be unique to this population and requires specific investigation.

There were three main limitations of this study, making it difficult to draw definite conclusions

from this study. First, the small sample size limits the generalizability of results. Second, the use of multiple outcomes to evaluate the effects of rehabilitation and the home exercise programme exposes the results to type I errors, with an increased likelihood of a false-positive finding. As adjusting for multiple comparisons increases the possibility of a type II error (reducing the power to detect a significant effect), this study reports unadjusted *P* values to reduce interpretation error.[35] Although the use of multiple outcomes generates this limitation, it has provided the opportunity to review the responsiveness of outcome measures to rehabilitation intervention.

The third limitation relates to the study design. A randomized cross-over controlled trial was applied for clinical equipoise[36] and to assist with recruitment to the study. This design required an overlap of treatment, between weeks 6 and 12; and 12 and 18, between groups. As a result, these data were analysed with a within-group statistical approach. This renders these result open to influence from external factors. However, the data between baseline and six weeks was conducted with a randomized controlled trial methodology to avoid bias, and as such the results can be attributed to the intervention.[37]

In this study, the motor domain of the Functional Independence Measure was the only objective measure of function to demonstrate a significant within-group change, even with an underpowered sample size. This suggests the motor domain of the Functional Independence Measure is a more sensitive outcome as compared with the Functional Independence Measure and should be considered as a primary outcome measure of function in future rehabilitation trials. This may be due to exclusion of non-motor measures of social cognition, present in the total Functional Independence Measure score, a redundant component given social cognition is unlikely to respond to physical rehabilitation.

This study highlights the difficulty in recruiting individuals with rare disease. In general, recruitment to rehabilitation clinical trials is difficult, with a large number of trials not meeting their endpoint due to inadequate recruitment.[38] Furthermore, rare diseases require considered planning and resources to ensure adequate study recruitment. This may include multicentre trials, international collaborations and biostatistical techniques to maximize data from small subject numbers.[39] In this study, the main barrier to participation was accessing the rehabilitation facility. Even shorter distances, considered reasonable to clinicians, may be troublesome for individuals with Friedreich's ataxia and other degenerative ataxias. If possible, funding should be acquired to support travel to the site of rehabilitation and multiple and easily accessible sites should be chosen for both rehabilitation services and the implementation of research.

Clinical messages

- A six-week intensive outpatient rehabilitation programme can improve health and well-being for individuals with Friedreich's ataxia.
- The motor domain of the Functional Independence Measure appears more specific in evaluating motor function as compared to the total score of the Functional Independence Measure.
- Home exercises appear ineffective in sustaining gains after six weeks of outpatient rehabilitation in individuals with Friedreich's ataxia.

Acknowledgements

The authors would like to thank all the participants who gave their time for this study. The authors would also like to thank the Kingston Centre Physiotherapy Department and Clinical Research Centre for Movement Disorders and Gait for their support during the study. The authors thank Jacinta Hussey, Beth Fivaz and Katrina Kenah for their dedicated work to provide the intervention and Kelly Saber, Charlotte Scroggie and Emma Campagna for their review of the rehabilitation intervention design. S.C.M. contributed to study concept and design, acquisition, analysis and interpretation of data, and drafting and revision of manuscript. L.A.C. contributed to study concept and design, analysis and interpretation of data, revision of manuscript for intellectual content and study supervision. M.R. contributed to acquisition of data and

revision of manuscript for intellectual content. A.M. contributed to study concept and design, analysis and interpretation of data and revision of manuscript for intellectual content. G.T. contributed to acquisition of data and revision of manuscript for intellectual content. N.G.-K. contributed to study concept and design, analysis and interpretation of data, revision of manuscript for intellectual content and study supervision. E.M.Y. contributed to study concept and design, revision of manuscript for intellectual content and study supervision. M.B.D. contributed to study concept and design, analysis and interpretation of data, revision of manuscript for intellectual content and study supervision.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: S.C.M. receives a National Health and Medical Research Council of Australia Postgraduate Scholarship (APP1093259). E.M.Y. receives a National Health and Medical Research Council of Australia Early Career Fellowship (APP1073323). M.B.D., L.A.C., N.G.-K., M.R. and A.M. report no disclosures.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This work was supported by the Bruce Lefroy Centre, Murdoch Children's Research Institute, Friedreich's Ataxia Association of Victoria, Friedreich's Ataxia Research Association (Australasia), Monash University and Friedreich's Ataxia Research Alliance (United States of America) and the Victorian Government's Operational Infrastructure Support Program. The supporting sources were not involved in the study design or conduct.

References

1. Milne SC, Corben LA, Georgiou-Karistianis N, et al. Rehabilitation for individuals with genetic degenerative ataxia: a systematic review. *Neurorehabil Neural Repair* 2017; 31: 609–622.
2. Synofzik M and Ilg W. Motor training in degenerative spinocerebellar disease: ataxia-specific improvements by intensive physiotherapy and exergames. *Biomed Res Int* 2014; 2014: 583507.
3. Maring J, Croarkin E, Morgan S, et al. Perceived effectiveness and barriers to physical therapy services for families and children with Friedreich ataxia. *Pediatr Phys Ther* 2013; 25: 305–313.
4. Ilg W, Schatton C, Schicks J, et al. Video game-based coordinative training improves ataxia in children with degenerative ataxia. *Neurology* 2012; 79: 2056–2060.
5. Ilg W, Synofzik M, Brotz D, et al. Intensive coordinative training improves motor performance in degenerative cerebellar disease. *Neurology* 2009; 73: 1823–1830.
6. Milne SC, Campagna EJ, Corben LA, et al. Retrospective study of the effects of inpatient rehabilitation on improving and maintaining functional independence in people with Friedreich ataxia. *Arch Phys Med Rehabil* 2012; 93: 1860–1863.
7. Seco CJ, Fernandez IG, Verdejol IC, et al. Improvements in Quality of Life in Individuals with Friedreich's Ataxia after Participation in a 5-Year Program of Physical Activity: an observational Study Pre-Post Test Design, and Two Years Follow-Up. *Int J Neurorehabil* 2014; 1: 129.
8. Miyai I, Ito M, Hattori N, et al. Cerebellar ataxia rehabilitation trial in degenerative cerebellar diseases. *Neurorehabil Neural Repair* 2012; 26: 515–522.
9. Chang YJ, Chou CC, Huang WT, et al. Cycling regimen induces spinal circuitry plasticity and improves leg muscle coordination in individuals with spinocerebellar ataxia. *Arch Phys Med Rehabil* 2015; 96: 1006–1013.
10. Beauchamp M, Labelle H, Duhaime M, et al. Natural history of muscle weakness in Friedreich's Ataxia and its relation to loss of ambulation. *Clin Orthop Relat Res* 1995; 311: 270–275.
11. Cruickshank TM, Reyes AR and Ziman MR. A systematic review and meta-analysis of strength training in individuals with multiple sclerosis or Parkinson disease. *Medicine (Baltimore)* 2015; 94: e411.
12. Kjølhede T, Vissing K and Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. *Mult Scler* 2012; 18: 1215–1228.
13. Sival DA, Pouwels ME, Van Brederode A, et al. In children with Friedreich ataxia, muscle and ataxia parameters are associated. *Dev Med Child Neurol* 2011; 53: 529–534.
14. Parkinson MH, Boesch S, Nachbauer W, et al. Clinical features of Friedreich's ataxia: classical and atypical phenotypes. *J Neurochem* 2013; 126: 103–117.
15. Delatycki MB and Corben LA. Clinical features of Friedreich ataxia. *J Child Neurol* 2012; 27: 1133–1137.
16. Burciu RG, Fritsche N, Granert O, et al. Brain changes associated with postural training in patients with cerebellar degeneration: a voxel-based morphometry study. *J Neurosci* 2013; 33: 4594–4604.
17. Aman JE, Elangovan N, Yeh IL, et al. The effectiveness of proprioceptive training for improving motor function: a systematic review. *Front Hum Neurosci* 2015; 8: 1075.
18. Leonardi L, Aceto MG, Marcotulli C, et al. A wearable proprioceptive stabilizer for rehabilitation of limb and gait ataxia in hereditary cerebellar ataxias: a pilot open-labeled study. *Neurol Sci* 2017; 38: 459–463.
19. Fonteyn EMR, Keus SHJ, Verstappen CCP, et al. The effectiveness of allied health care in patients with ataxia: a systematic review. *J Neurol* 2014; 261: 251–258.
20. Galea CA, Huq A, Lockhart PJ, et al. Compound heterozygous FXN mutations and clinical outcome in Friedreich ataxia. *Ann Neurol* 2016; 79: 485–495.

21. Subramony SH, May W, Lynch D, et al. Measuring Friedreich ataxia: interrater reliability of a neurologic rating scale. *Neurology* 2005; 64: 1261–1262.
22. Hsueh IP, Lin JH, Jeng JS, et al. Comparison of the psychometric characteristics of the functional independence measure, 5 item Barthel index, and 10 item Barthel index in patients with stroke. *J Neurol Neurosurg Psychiatry* 2002; 73: 188–190.
23. Cano SJ, Riazi A, Schapira AH, et al. Friedreich's ataxia impact scale: a new measure striving to provide the flexibility required by today's studies. *Mov Disord* 2009; 24: 984–992.
24. Tai G, Yiu EM, Corben LA, et al. A longitudinal study of the Friedreich Ataxia Impact Scale. *J Neurol Sci* 2015; 352: 53–57.
25. Hurst H and Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. *J Manipulative Physiol Ther* 2004; 27: 26–35.
26. Kiresuk TJ and Sherman RE. Goal attainment scaling: a general method for evaluating comprehensive community mental health programs. *Community Ment Health J* 1968; 4: 443–453.
27. Berg K, Wood-Dauphinee S, Williams JI, et al. Measuring balance in the elderly: preliminary development of an instrument. *Physiother Canada* 1989; 41: 304–311.
28. Boyd RN and Graham HK. Objective measurement of clinical findings in the use of botulinum toxin type A for the management of children with cerebral palsy. *Eur J Neurol* 1999; 6: s23–s35.
29. Cornwall MW, McPoil TG, Lebec M, et al. Reliability of the modified Foot Posture Index. *J Am Podiatr Med Assoc* 2008; 98: 7–13.
30. Gill DP, Jones GR, Zou GY, et al. The Phone-FITT: a brief physical activity interview for older adults. *J Aging Phys Act* 2008; 16: 292–315.
31. Young Y, Fan MY, Hebel JR, et al. Concurrent validity of administering the functional independence measure (FIM) instrument by interview. *Am J Phys Med Rehabil* 2009; 88: 766–770.
32. Delatycki MB, Holian A, Corben L, et al. Surgery for equinovarus deformity in Friedreich's ataxia improves mobility and independence. *Clin Orthop Relat Res* 2005; 430: 138–141.
33. Cassidy E, Naylor S and Reynolds F. The meanings of physiotherapy and exercise for people living with progressive cerebellar ataxia: an interpretative phenomenological analysis. *Disabil Rehabil*. Epub ahead of print 6 February 2017. DOI: 10.1080/09638288.2016.1277400.
34. Bossie HM, Willingham TB, Schoick RAV, et al. Mitochondrial capacity, muscle endurance, and low energy in Friedreich ataxia. *Muscle Nerve* 2017; 56: 773–779.
35. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990; 1: 43–46.
36. Deng C, Hanna K, Bril V, et al. Challenges of clinical trial design when there is lack of clinical equipoise: use of a response-conditional crossover design. *J Neurol* 2012; 259: 348–352.
37. Sullivan GM. Getting Off the 'Gold Standard': randomized Controlled Trials and Education Research. *J Grad Med Educ* 2011; 3: 285–289.
38. Blanton S, Morris DM, Prettyman MG, et al. Lessons learned in participant recruitment and retention: the EXCITE trial. *Phys Ther* 2006; 86: 1520–1533.
39. Griggs RC, Batshaw M, Dunkle M, et al. Clinical research for rare disease: opportunities, challenges, and solutions. *Mol Genet Metab* 2009; 96: 20–26.