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

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Abstract

Purpose: To determine the effects of a physical activity-based rehabilitation focused on quality of life in individuals with FA who completed a five-year program.

Methods: The study design was longitudinal and observational with pre- and post-test assessments, and two years follow-up. We studied 16 patients with FA. Participants received pharmacological treatment and took part in a physical activity rehabilitation program (intervention group) or received pharmacological treatment alone (controls). They were all assessed using the International Cooperative Ataxia Rating Scale (ICARS), SF-36 Health Survey and Functional Independence Measure (FIM). Changes over time and differences between groups were assessed with repeated measure analysis of variance (ANOVA) and Student’s t-tests.

Results: In the intervention group, a change in the distribution of the mean ICARS score from 93.10±4.63 to 94.90 ± 4.50 suggested a slight worsening in ataxia (not significant). In contrast, the means on the SF-36 (43.89 ± 5.55 to 51.70±4.19) and FIM (50.20±16.02 to 59.20±15.01) both increased significantly over time. That is, after the treatment, patients in the intervention group showed a significant improvement in communication, daily living skills and socialization, and the improvement in their quality of life was maintained at the two-year follow-up.

Conclusions: Long-term rehabilitation improved physical capacity and health-related quality of life. This study provides evidence for maintaining long-term physical activity programs in institutionalized patients with FA.

Keywords: Friedreich’s ataxia; ICARS; SF-36; FIM; Rehabilitation

Introduction

In Europe, the prevalence of childhood ataxias was estimated to be 26/100,000 children, a rate that is likely to be among the lowest in the world [1]. Among these, Friedreich’s ataxia (FA) is one of the most prevalent forms of autosomal recessive ataxia. It is a neurodegenerative disorder characterized by progressive limb and gait ataxia, dysarthria, diminished or absent deep tendon reflexes and loss of proprioception [2-4]. The neurological phenotype reflects lesions in dorsal root ganglia, sensory peripheral nerves, corticospinal tracts, and dentate nuclei [4,5].

The affected gene, FXS, is located on chromosome 9p. The mutation is an intronic expansion of GAA triplets. In the normal version of the gene, the number of GAA repeats ranges from 8 to 22, while in FA there are from 200 to as many as 1,700. Since the discovery of the mutation in the FXN gene that causes FA [6], a wide spectrum of clinical manifestations of the condition have been reported [7]. Given this, multiple concomitant features have to be considered to assess the phenotype of the disease [8]. These may include non-neurological features such as scoliosis, diabetes mellitus and hypertrophic cardiomyopathy. Indeed, cardiomyopathy is a severe and often life-limiting manifestation of FA [9].

The disease is believed to be caused by reduced expression of frataxin. Progressive neurodegeneration in FA is mediated by mutant proteins capable of inducing neuronal damage and synaptic neurotransmission deficits by interfering with several conserved cellular and molecular pathways including protein aggregation and clearance, dysregulation of transcription and gene expression, the ubiquitin–proteasome system, alterations of calcium homeostasis, and activation of pro-apoptotic routes among others [10].

Currently, research is underway to evaluate the efficacy and effectiveness of several drug treatments and gene therapies developed on the basis of the pathogenesis of the disease [11]. For example, the generation of induced pluripotent stem cell lines derived from FA patients, following correction of the mutated gene, could provide a useful source of immune-compatible cells for transplantation therapy [12]. However, rehabilitation and physical therapy still play a dominant role in the clinical management of FA patients [13]. In spite of this, it was noted in a review that there are no valid data on the real value of physical activity and psychological support as treatments for degenerative ataxia [5]. In addition, degenerative diseases are especially difficult to treat because of their progressive nature and their effect on virtually all parts of the cerebellum. There are few medical options for treating ataxias and those available are only suitable for specific forms of the disease and symptoms [14]. Furthermore, motor rehabilitation is also challenging for this patient population because of the aforementioned functional role of the cerebellum in motor learning and motor adaptation. In particular, damage to structures critically involved in relearning of motor skills may result in poor recovery or limited benefit from physiotherapeutic training [14].

On the other hand, the principle of physiotherapeutic intervention is to activate and demand control mechanisms for balance control and multi-joint coordination. In this regard, a role may be played by neural

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plasticity mechanisms, which have been well studied and characterized in the cerebellum [15]. Furthermore, interventions train patients’ ability to select and use visual, somatosensory, and vestibular inputs to preserve and retrain their capability to react to unforeseen situations and, as far as possible, to avoid falls. However, relatively few clinical studies have evaluated physiotherapeutic interventions for patients with cerebellar ataxia, most that have been reported consisting of single cases or very small patient populations with different types of cerebellar disease and severity of ataxia [16,17]. On the other hand, Hatakenaka et al. [18] demonstrated that, for ataxic patients with infratentorial stroke, the degree of impaired motor learning is correlated with reduced long-term rehabilitation gains. Thus, long-term rehabilitation studies in humans are needed to establish whether these promising results also hold for FA patients [19].

Onset of FA typically occurs in late childhood or early adolescence, but is variable. Its clinical progression is slow, with an average time from onset to death of approximately 36 years, though the range is as wide as 5 to 71 years; the rate of progression varying between individuals and also between phases of the disease. Even though mobility seems to deteriorate faster in females, no sex differences in life expectancy have been reported.

A range of approaches can be used to assess patients with FA. The International Cooperative Ataxia Rating Scale (ICARS) was designed to evaluate clinical disability in patients with cerebellar ataxia and has been tested in patients with FA [20]. In general, health-related quality of life (HRQOL) assessments provide valuable clinical information in clinical trials and other research on neurological disorders. Indeed, though neurological examinations are useful for the diagnosis of FA, HRQOL questionnaires capture the patients’ perspective, and may represent the only method for measuring improvement or progression in patients with severe impairment. The Short Form-36 (SF-36) questionnaire is a standardized and widely-used generic scale for assessing mental and physical aspects of HRQOL, while the Functional Independence Measure (FIM) scale assesses physical and cognitive disability [4]. In this study, we used a general HRQOL measure, namely the SF-36, combined with ICARS and the FIM to describe activity limitation in FA.

Given all this, the main objectives of this study were to determine whether there were improvements in quality of life in institutionalized individuals with FA who completed a five-year rehabilitation program and, if so, whether these improvements were sustained over time.

Methods

Design

The study design was longitudinal, with pre- and post-test assessments and it ran from January 2005 until January 2010 with two years of follow-up.

Patients

We studied 16 institutionalized patients with FA from the region of Castilla y León (Spain). The diagnosis of FA, made on the basis of their medical history and a physical and neurological examination, was then genetically confirmed. Patients with FA were assessed for eligibility and recruited through the health care unit of the center where they were routinely cared for before the start of the study. The centers involved were Las Cinco Lagunas Social Center, Fisioterapia Clinic, El Pilar Medical Center, and Hogar 70 Residence, all in Castilla y León. These are residential centers for the promotion of personal autonomy and support for dependent individuals with severe disabilities, in the region of Castilla y León (Spain). The intervention groups were all cared for throughout the study at Las Cinco Lagunas Social Center, while those from the control group were cared for in one of the other centers, and hence, there was no contact between the groups during the study. Moreover, different staff worked at the different centers, and they were not informed about the existence of the other group. Specifically, once the full sample had been recruited, all the participants included in the intervention group were transferred to Las Cinco Lagunas Center (Astorga, Spain) for the duration of the study and follow-up. That is, all participants included in the intervention group received their treatment in the same center throughout the study.

Inclusion criteria

As well as having a clinical diagnosis of FA, inclusion criteria were being on a stable medication regimen (no changes over the previous 3 months) and neurologically symptomatic. All participants underwent medical screening and physical examination prior to enrolment. The data collected allowed a general health assessment to be made, in order to ensure early identification of any absolute or relative contraindications to, or limitations on, treatment involving exercise. Their medical history was taken using a standardized protocol.

Exclusion criteria

Patients were excluded on the basis of medical records: in addition to meeting the inclusion criteria, it was required that patients had no serious concomitant illnesses, such as active arrhythmia, significant heart failure, or dementia. Failure in a previous physical condition examination, absence from more than 20% of rehabilitation sessions, and refusal to sign the consent form and/or attendance register were also considered reasons for exclusion.

After giving informed consent, the candidates who met all of the inclusion and none of the exclusion criteria were assigned a number according to a block randomization scheme [21]. Specifically, participants were randomly allocated, using the Quick Calcs application in Graph Pad Software®, to one of two treatment groups: the control group (n = 6; 48.17 years old; 3 women; 3 men) received the usual pharmacological treatment, while the intervention group (n = 10; 56.4 ± 4.061 years old; 4 women; 6 men) participated in a physical activity program as well as receiving pharmacological treatment (both detailed below). That is, the controls were not exposed to the specific new physiotherapy program followed by those in the intervention group. Given the ethical implications, it was not considered possible to have a control group of patients with Friedreich’s ataxia that received no drug treatment.

The flow of patients through each stage of the study is shown in Figure 1. To investigate the effects of rehabilitation (health care and physical activity) on quality of life, the participants were assessed pre- and post the five-year treatment period and again two years later. All participants agreed to come back after two years for the follow-up assessment.

Ethical considerations

The study was designed in accordance with the recommendations for clinical research of the Declaration of Helsinki of the World Medical Association of 1975 as revised in 1983. In line with these requirements, the procedure and the study protocol were explained to all potential participants and they or their legal guardians (in the case of individuals who lacked the mental capacity to decide) gave...
written informed consent before inclusion. The protocol was reviewed and approved by the local ethics committees for the social centers and the University of León.

Outcomes

The participants were assessed using the FIM, SF-36 and ICARS on the day before starting the treatment, at the end of the treatment period and at two years follow-up. The total scores of these scales have been shown to be reliable and valid for assessing disease status [2-4,22].

As recommended by other authors [23]. Caring for individuals with FA, the scales were administered in a single, one-hour session, to minimize the effects of fatigue and thereby maximize accuracy. Further, for all participants, this single session was at the same time of day and instruments were administered in the same order, to minimize intra-subject variability. The doctors who administered the questionnaires were blinded to the treatment given and the scores participants obtained. To limit the influence of external factors, as well as all the assessments, the intervention was carried out at the same time of day, at the same room temperature and by one of two physiotherapists specializing in rehabilitation.

In addition to the aforementioned doctors and physiotherapists, care providers were blinded to treatment allocation, as were participants themselves, and the researchers, including those who carried out the data analysis (who were unaware of the group allocation for the data they were processing). That is, we attempted to ensure integrity of the blind by using different individuals to provide the treatment and assess the outcomes, and further, all participants signed a confidentiality statement stating explicitly that they would not speak to the other participants at any point during the study.

Rehabilitative treatment

All participants received the usual pharmacological treatment (Appendix 1). There were no changes in participants’ medications over the course of the study, with the exception of modification of the Acenocumarole 4 mg (Sintron®) dose in the two patients on this drug.

In addition, the intervention group participated in a rehabilitation (healthcare and physical activity) program for FA. Neither rehabilitation specialist knew the group allocation of individuals they were treating.

These physiotherapists carried out the intervention following guidelines published in the literature [5,7]. Furthermore, this treatment had the usual objectives of a physical program in such patients [23-26]. Specifically, the objective of each physical session was to develop the patients’ functional capacity (aerobic capacity, flexibility, upper and lower limb strength, motor coordination and balance). Rhythmic activities, functional and balance retraining, stretching exercises, occupational and recreational activities were all included in the treatment. Participants were instructed to focus their attention on carrying out each exercise. Table 1 provides an overview of the physical rehabilitation program for ataxia at the International Center for Neurological Restoration on which our intervention was based. The program consisted of 60-minute sessions, three times a week over a 5-year period, with two 1-week breaks a year, one in the summer and one in the Christmas/New Year period. Each session had four parts: general physical condition, specific physical condition, pre-functional training, and functional training (the functional capacity components mainly being covered during the core activities).

Statistical analysis

Data obtained from all participants showed a normal distribution and were expressed as mean ± standard deviation (SD).

| Stage                        | Objective                                                                 | Activities                                           |
|------------------------------|---------------------------------------------------------------------------|------------------------------------------------------|
| General physical condition   | Reduction of cerebrovascular reactivities. Improve muscular tone and increase respiratory capacity and general fitness and working capacity | Infrared thermotherapy. Therapeutic massage. Breathing exercises. Passive, active, and resisted kinesiotherapy. Ideomotor training. Exercises to reduce rigidity. Exercises for general physical condition |
| Specific physical condition  | Consolidate achievements of the previous step. Improve coordination (proprioception, equilibrium, rhythm, and precision). Improve posture. Increase force | Coordination exercises. Exercises for posture. Exercises with weight. |
| Prefunctional training       | Consolidate previous achievements. Training in static and dynamic gait patterns. Increase resistance | Training of gait. Body postural transfers. Static and dynamic equilibrium. Mechanotherapy, shoulder wheel and hand table therapy |
| Functional training          | Consolidate previous achievements. Improve equilibrium, coordination, and rhythm. Improve gait function | Coordination training (activities with balls). Motorized movement therapy machine, for lower and upper extremities (artromotor Motomed®) |

Table 1: Overview of the physiotherapy program for institutionalized patients with ataxia at the Cinco Llagas Center for institutionalized patients.
The normality of all distributions was test using the Shapiro-Wilk test. Repeated measure analysis of variance (ANOVA) was carried out to assess whether there were significant variations in parameters over the course of the study. Differences were considered statistically significant when P ≤ 0.05 (while the threshold was set at 0.01 for the other analysis). Paired Student’s t tests were used to analyze differences over time. A contingency table with a chi-square test confirmed that there were significant differences in sex ratios between control and intervention groups.

Statistical analyses were performed using the IBM SPSS (Version 21, Armonk, NY, USA).

Results

Finally, we evaluated 16 patients diagnosed with FA: 7 women and 9 men with mean ages of 53.31 ± 5.654 years at the start of the study and 12.33 ± 1.821 years at diagnosis. We had two losses to follow-up from the intervention group: one individual withdrew due to medical complications and another discontinued the intervention.

All the patients had pyramidal signs and absence of reflexes in the lower extremities; seven of them had various degrees of cardiomyopathy and four had diabetes mellitus; none of the patients had a history of toxic exposure. Other demographic and clinical characteristics of patients are described in Table 2.

A lack of statistically significant differences was observed between no intervention and intervention groups in relation to the variables “sex” (Pearson’s chi-square test, p value =0.696) and history of FA (Student’s t test, p=0.399) (Table 2). In both groups, for all three scales, the Shapiro-Wilk test p-values were greater than the chosen alpha level (0.05) indicating that the residuals are approximately normally distributed (Appendix 2).

Regarding the comparison of means between the groups (Table 3), the data shown in the table indicate that the values obtained in the intervention group for the three scales at all the time points (2005, 2010 and 2012) are not consistent with a mean of zero, while those obtained in the controls tends to zero.

This was also found comparing the means with the Student’s t-tests (Appendix 3).

Comparing the mean (standard deviation) scores on the FIM (Figure 2) in the control and the intervention groups, ANOVA revealed that the mean scores at the start of the study were higher in the controls, indicating that the controls had less activity limitation than those in the intervention group at baseline. By the end of the study, though their scores were still higher, the difference was smaller. What is more, by 2 years of follow-up the situation had reversed, with scores of the intervention group increasing relative to their scores at earlier time points and becoming higher than those of controls, suggesting that the degree of activity limitation decreased over time in those who received the physiotherapy intervention.

No significant differences were found in the SF-36 scores between the groups at baseline at the end of the study or 2 years later.

Regarding the ICARS scores, participants obtained similar mean scores in the two groups at baseline, indicating that they had a similar degree of activity limitation. By the end of the intervention, however, the mean scores in the controls had increased, the scores showing that activity was limited among controls than those in the intervention group. That is, the participants who received the physiotherapy intervention seemed to have a better course over time.

We also calculated the p value for the comparison between the mean scores on the FIM, SF-36 and ICARS, in the three different time points; pre-test; post-test; and at 2 years of follow-up (Figure 3). Among these clinical measures, the mean FIM and SF-36 scores had decreased by the end of the treatment period in the controls, and tended to fall further at the 2-year follow-up, the mean scores on the FIM showing an increasing dependence and those on the SF-36 a worsening health status (Figure 3) in this group. An increasing dependence in the control group was also reflected in the mean ICARS scores, which had increased by the end of the treatment period and were even higher 2 years later.

Figure 3 also shows the mean scores on these scales for the intervention group. In contrast to the controls, mean scores on the FIM in this group increased from the start to the end of the treatment period, indicating a higher level of independence, but decreased slightly over the follow-up, though not to as low as the initial values (Figure 3). Specifically, comparing the baseline and final scores, dependence tended to have decreased over the study period (the mean FIM score increasing from 50.20 ± 16.02 to 59.20 ± 15.01). Mean SF-36 scores fell from the beginning to the end of the treatment period in the intervention group, which suggests that their health status worsened, and this trend continued over the 2-year follow-up period.

Further, the mean ICARS scores did not vary significantly from the start to the end of the treatment period, remaining similar at the end of the follow-up (Figure 3). This could be interpreted as a plateauing of the degree of dependence of those who received the intervention. Appendix 4 summarizes the main descriptive statistics of the studied variables.

Discussion

Our study showed that it is possible for the quality of life of
Figure 2: Comparison among the means (± standard deviation) of the control and the intervention group for the Functional Independence Measure (FIM) scale, the 36-item Short Form Health Survey (SF-36) and the International Cooperative Ataxia Rating Scale (ICARS) scores. ANOVA was performed for the three time points: (A) pre-test, 2005; (B) post-test, 2010; and (C) at 2 years of follow-up.

Figure 3: Comparison among the means (± standard deviation) of the International Cooperative Ataxia Rating Scale (ICARS), Functional Independence Measure (FIM) and 36-item Short Form Health Survey (SF-36) scores at the different time points: pre-test, 2005; post-test, 2010; and 2 years of follow-up. The control and the intervention group were analyzed separately. Paired Student’s t-tests were used to analyze the differences.
Institutionalized patients with FA to improve and those improvements can be sustained, at least for 2 years. Milne et al. [27] reported the first evidence that a period of inpatient rehabilitation improves or halts the downward decline in function for people with FA, and recently it has been found that cerebellar patients with ataxia can benefit from a home exercise program focused on balance training [13]; our results build on their findings, showing that these benefits are more than just short-term achievements.

Of the available HRQOL questionnaires, the one that seems most appropriate for degenerative ataxias is the SF-36: in particular, this generic questionnaire has shown its usefulness in certain rare diseases with some clinical, progression and prognosis similarities with degenerative ataxia [5]. Riazi et al. [28] defended the use of self-report questionnaires in FA to assess aspects of outcome not captured with degenerative ataxia [5]. The ICARS scale is not appropriate for evaluating the progression of FA in patients with long disease durations; further, as in other studies [22] they also advise against its use due to the fact that the sensitivity of the ICARS is very dependent on the sample size. Nevertheless, it has been emphasized that the patient’s perspective should be considered to improve the quality of research in this field [5], that a full range of relevant health outcome measures should be included [31] and, in particular, that HRQOL measurements should always be included as a part of trial design [32]. Therefore, we considered that an important first step in improving patient-based outcome measurement in FA is to evaluate the potential usefulness of existing widely-used rating scales [32]. In particular, the precise characterization of impairments and limitations with sensitive and well-validated tools has the potential to assist in the evaluation of the efficacy of new interventions under consideration [24]. Taken together, comprehensive interviews and body system assessments are important for evaluating the clinical manifestations and impact of this disease, which affects multiple systems [9].

On the other hand, the benefits of physical programs have been demonstrated for other patient populations with disabling degenerative conditions [33] including ataxia [24] and it seemed reasonable to suppose that the health and function of people with FA would also benefit from regular participation in a tailored exercise program [24], particularly given that the strategy of the physiotherapeutic interventions was to activate and challenge control mechanisms for balance control and multi-joint coordination [14]. Furthermore, our intervention trained the patients’ ability to select and use visual, somatosensory, and vestibular inputs to preserve and retrain patients’ capability for reacting to unforeseen situations.

There is considerable evidence to support the network perspective for describing and explaining brain function, giving rise to theories such as the universal control system, [34] and the concept of synaptic homeostasis for the stabilization of neuronal circuits [35]. One of the things we know about neural plasticity is that it is enhanced by new behavioral learning, rather than just repetition of exercises/activities in the absence of learning [36], supporting the hypothesis that’s implementor activity is insufficient to produce long-term plasticity in cortical representations. In turn, this would explain the clinical improvement observed following participation in physical programs, the improvement being attributable to the plasticity of the central nervous system, which ensures that when certain neurons lose their function, others take over their role [37–40]. Further, voluntary learning and re-learning of lost or impaired skills, by the continuous repetition of tasks requiring neurological functions affected by the disease and retraining of functional patterns, could also improve the quality of life of these patients [37–40]. In particular, stimulation of proprioceptive pathways could improve balance. Indeed, it has been described that mechanical vibration of the muscle induces an involuntary contraction reflex called a ‘tonic vibration reflex’ [41], while it has also been demonstrated that individuals with mild cerebellar ataxia organize feed-forward postural muscle synergies and show more co-contraction modes and impaired coordination during feedback and feed-forward postural control [42].

While most scientists agree that the large inclusions seen inside neurons in disease brain are not the primary culprit causing neurons to die, they do represent a pathological hallmark reflecting a chronic problem with protein homeostasis [43]. In the current scientific

### Table 3: Comparison of the mean scores in the International Cooperative Ataxia Rating Scale (ICARS), the Functional Independence Measure (FIM) scale and the 36-item Short Form Health Survey (SF-36) in the intervention and control (no intervention) groups.

| Measure                  | Group          | p-value |
|--------------------------|----------------|---------|
| ICARS score 2005         | Control group | 0.839   |
|                          | Intervention   |         |
| ICARS score 2010         | Control group | 0.000** |
|                          | Intervention   |         |
| ICARS score 2012         | Control group | 0.000** |
|                          | Intervention   |         |
| FIM 2005                 | Control group | 0.655   |
|                          | Intervention   |         |
| FIM 2010                 | Control group | 0.362   |
|                          | Intervention   |         |
| FIM 2012                 | Control group | 0.053   |
|                          | Intervention   |         |
| SF36 HealthSurvey, 2005  | Control group | 0.103   |
|                          | Intervention   |         |
| SF36 HealthSurvey, 2010  | Control group | 0.604   |
|                          | Intervention   |         |
| SF36 HealthSurvey, 2012  | Control group | 0.254   |
|                          | Intervention   |         |

**p<0.01
Discussion on treatment strategies in neurodegenerative diseases such as FA, the physical treatment and functional approaches play an increasingly important role because it is recognized that the early phases of neurodegeneration are characterized by neuronal dysfunction, while impaired neuronal cell metabolism and cell death are events that occur later in the disease course. It is also conceivable that early interference with neuronal dysfunction may not only temporarily improve symptoms, but also have a disease modifying effect [43]. It may be that physical therapy plays an important role in the regulation of neuronal activity in the cerebellar cortex and deep cerebellar nuclei.

With respect to our present study, we recognize the small sample size to be a limitation. Hence, while our results contribute to the evidence that therapy does have some positive effects (HRQOL improvement), more research is required in this field with larger sample sizes. Another limitation is that we conducted assessments, at baseline, after five-year of intervention, and again after two years of follow-up but none mid-treatment; that is, though it seemed reasonable to consider these lengths of treatment as they are the same as those used in other studies with similar patients [13,16,17], we did not collect interim data that would have enabled the tracking changes or variability. The fact that the participants in our study were institutionalized minimized interference from potential benefit that could be derived from social interaction related to travelling from home to a center to receive treatment. Nevertheless, it cannot be completely ruled out that observed improvements in quality of life are related to the social interaction associated with the intervention.

In the literature, there is little evidence on the benefits of exercise in people with FA. On the other hand, at present this disease has no cure, and it is clearly desirable for patients to maintain the best possible level of wellness. Hence, more research and translation to practice are needed in the field of rehabilitation to achieve this objective. For future investigations in this area maybe sEMG of muscle activity, biothesiometer studies to assess vibration perception at baseline and post PA programme should be conducted to determine if there are any changes in muscle activity patterns and vibration perception in such populations. In addition, a sensor and programme now available to assess stability (dorsaVi-Move) which can provide quantitative balance feedback as well as assist in balance training in many patient populations including FA patients.

To the best of our knowledge, this is the first study to systematically evaluate the HRQOL of individuals with FA associated with participation in a group institutional rehabilitation program (involving healthcare and physical activity), with follow-up (of two years) to explore whether benefits are sustained. The institutional program may also provide a means to optimize the use of financial and health care resources in the face of the often functionally limiting progressive disease of FA.

Conclusion
We found significant improvements in quality of life in individuals with FA who completed a five-year healthcare and physical activity program, suggesting that long-term rehabilitation programs are useful in these patients. In particular, compared to no-intervention controls, participants in the program had significantly better HRQOL after the intervention and again after a two-year follow-up. These benefits seem to be associated with the long-term healthcare and physical activity. That is, the clinical impact observed is evidence in favor of maintaining long-term healthcare programs with physical activity in patients with FA.

Declaration of Interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

IG and JS contributed the concept/idea/project/design and writing, while JTU, VR and IC are involved in the discussion and the review and critique of the manuscript, and AFA are carried out the statistical analysis.

Key Messages

What is already known on this topic
Rehabilitation still plays a dominant role in the clinical management of FA patients. In the literature, there is little evidence of benefits of exercise in people with FA. Further, no previous studies have provided valid data on the real value of long-term rehabilitation programs as treatments for degenerative ataxia. On the other hand, at present this disease has no cure, and it is clearly desirable for patients to maintain the best possible level of wellness.

What this study adds
To the best of our knowledge, this is the first study to systematically evaluate the HRQOL of individuals with FA associated with participation in a group institutional rehabilitation program (involving health care and physical activity), with follow-up (of two years) to explore whether benefits are sustained. The institutional program may also provide a means to optimize the use of financial and health care resources in the face of the often functionally limiting progressive disease of FA.

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References
1. Musselman KE, Stoyanov CT, Marasigan R, Jenkins ME, Konczak J, et al. (2014) Prevalence of ataxia in children: a systematic review. Neurology 82: 80-89.
2. Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, et al. (1997) International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. J Neurol Sci 145: 205-211.
3. Newnham EA, Harwood KE, Page AC (2007) Evaluating the clinical significance of responses by psychiatric inpatients to the mental health subscales of the SF-36. J Affect Disord 98: 91-97.
4. Keith RA, Granger CV, Hamilton BB, Sherwin FS (1987) The functional independence measure: a new tool for rehabilitation. Adv Clin Rehabil 1: 6-18.
5. Trujillo-Martín MM, Serrano-Aguilar P, MONTÓN-ALVAREZ F, Carrillo-Fumero R (2009) Effectiveness and safety of treatments for degenerative ataxias: a systematic review. Mov Disord 24: 1111-1124.
6. Campuzano V, Montermini L, Moltó MD, Pianese L, Cossée M, et al. (1996) Friedrich’s ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 271: 1423-1427.
7. Hou JG, Jankovic J (2003) Movement disorders in Friedrich’s ataxia. J Neurol Sci 206: 59-64.
8. Epstein E, Farmer JM, Tsou A, Perlman S, Subramony SH, et al. (2008) Health related quality of life measures in Friedreich Ataxia. J Neurol Sci 272: 123-128.
9. Meyer C, Schmid G, Göritz S, Ernst M, Wilkens C, et al. (2007) Cardiomyopathy in Friedreich’s ataxia—assessment by cardiac MRI. Mov Disord 22: 1615-1622.
10. Matilla-Dueñas A, Sánchez I, Corral-Juan M, Dávalos A, Alvarez R, et al. (2010) Cellular and molecular pathways triggering neurodegeneration in the spinocerebellar ataxias. Cerebellum 9: 148-166.
11. Voncken M, Ioannou P, Delatycki MB (2004) Friedreich ataxia-update on pathogenesis and possible therapies. Neurogenetics 5: 1–8.

12. Liu X, Verma PJ, Evans-Gales MV, Delatycki MB, Michalska A, et al. (2011) Generation of induced pluripotent stem cell lines from Friedreich ataxia patients. Stem Cell Rev 7: 703–713.

13. Keller JL, Bastian AJJ (2014) A home balance exercise program improves walking in people with cerebellar ataxia. Neurorehabil Neural Repair 28: 770–778.

14. Ilg W, Timmann D (2013) Gait ataxia--specific cerebellar influences and their rehabilitation. Mov Disord 28: 1566–1575.

15. Jorge-Rodriguez JL, Fernández-Martínez E, Rodríguez D, Peralta-Flores A, Bergado JA, et al. (2013) Motor improvement in cerebellar ataxia after interventional rehabilitation. Journal of Neurorehabilitation 1: 31–36.

16. Ilg W, Timmann D (2013) General management of cerebellar disorders: an overview. In: Manto M, Schmahmann J, Rossi F, Grati D, Kolbuchi N, eds. Handbook of the Cerebellum and Cerebellar Disorders. Amsterdam, the Netherlands: Springer; 2349–2368.

17. Marsden J, Harris C (2011) Cerebellar ataxia: pathophysiology and rehabilitation. Clin Rehabil 25: 195–216.

18. Hatakenaka M, Miyai I, Mihara M, Yagura H, Hattori N (2012) Impaired motor learning by a pursuit rotor test reduces functional outcomes during rehabilitation of poststroke ataxia. Neurorehabil Neural Repair 26:293–300.

19. Ribai P, Poussel F, Tanguy ML, Rivaud-Pechoux S, Le Ber I, et al. (2007) Neurological, pathological, and ocoulomotor progression in 104 patients with Friedreich ataxia during long-term follow-up. Arch Neurol 64: 558–564.

20. Cano SJ, Hobart JC, Hart PE, Korlipara LV, Schapira AH, et al. (2005) International Cooperative Ataxia Rating Scale (ICARS): appropriate for studies of Friedreich’s ataxia? Mov Disord 20: 1585–1591.

21. Plantadios S (1997) Clinical Trial: a Methodologic Perspective. New York: John Wiley & Sons.

22. Fahey MC, Corben L, Collins V, Churchyard AJ, Delatycki MB (2007) How is disease progress in Friedreich’s ataxia best measured? A study of four rating scales. J Neurol Neurosurg Psychiatry 78: 411–413.

23. Drinkard BE, Keyser RE, Paul SM, Arena R, Plehn JF, et al. (2010) Exercise capacity and idebenone intervention in children and adolescents with Friedreich ataxia. Arch Phys Med Rehabil 91: 1044–1050.

24. Maring JR, Croarkin E (2007) Presentation and progression of Friedreich ataxia and implications for physical therapist examination. Phys Ther 87: 1676–1696.

25. Harris-Love MO, Siegel KL, Paul SM, Benson K (2004) Rehabilitation management of Friedreich ataxia: lower extremity force-control variability and gait performance. Neurorehabil Neural Repair 18:117–124.

26. Friedman LS, Farmer JM, Perlman S, Wilnott G, Gomez CM, et al. (2010) Measuring the rate of progression in Friedreich ataxia: implications for clinical trial design. Mov Disord 25: 426–432.

27. Milne SC, Campagna EJ, Corben LA, Delatycki MB, Teo K, et al. (2012) Retrospective study of the effects of rehabilitation on improving and maintaining functional independence in people with Friedreich ataxia. Arch Phys Med Rehabil 93: 1860–1863.

28. Riazi A, Cano SJ, Cooper JM, Bradley JL, Chaparta AH, et al. (2006) Coordinating outcomes measurement in ataxia research: do some widely used generic rating scales tick the boxes? Mov Disord 21: 1398–1453.

29. Wilson CL, Fahey MC, Corben LA, Collins VR, Churchward AJ, et al. (2007) Quality of life in Friedreich ataxia: what clinical, social, and demographic factors are important? Eur J Neurol 14: 1040–1047.

30. Delatycki MB (2009) Evaluating the progression of Friedreich ataxia and its treatment. J Neurol 256 Suppl 1: 36–41.

31. Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, et al. (2004) Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach. Health Technol Assess 8: 1–148, Ill–IV.

32. La Pean A, Jefferies N, Grow C, Ravina B, Di Prospero NA (2006) Predictors of progression in patients with Friedreich ataxia. Mov Disord 23: 2026–2032.

33. Pérez-Avila I, Fernández-Veitez JA, Martínez-Góngora E, Ochoa-Mastrapa R, Velázquez-Manresa MG (2004) Effects of a physical training program on quantitative neurological indices in mild stage type 2 spinocerebellar ataxia patients. Rev Neurol 39: 907–910.

34. Kazantsev VB, Nekorkin VI, Makarenko VI, Llinás R (2003) Olivocerebellar cluster-based universal control system. Proc Natl Acad Sci U S A 100: 13064–13068.

35. Turrigiano G (2007) Homeostatic signaling: the positive side of negative feedback. Curr Opin Neurobiol 17: 318–324.

36. Plautz EJ, Milliken GW, Nudo RJ (2000) Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. Neurobiol Learn Mem 74: 27–55.

37. Bishop B (1982) Neural plasticity. Part 4. Lesion-induced reorganization of the CNS: recovery phenomena. Phys Ther 62: 1442–1451.

38. Schalow G, Zäch GA (2000) Reorganization of the human central nervous system. Gen Physiol Biophys 19 Suppl 1: 11–240.

39. Lundy-Ekman L (2002) Neuroscience: fundamentals for rehabilitation. 2nd Ed. Philadelphia: WB Saunders.

40. Fujiwara T, Kasashima Y, Honaga K, Murakoa Y, Tsuji T, et al. (2009) Motor improvement and corticospinal modulation induced by hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy in patients with chronic stroke. Neurorehabil Neural Repair 23: 125–132.

41. Herrero AJ, Martín J, Martín T, García-López D, Garatachea N, et al. (2011) Whole-body vibration alters blood flow velocity and neuromuscular activity in Friedreich’s ataxia. Clin Physiol Funct Imaging 31: 139–144.

42. Asaka T, Wang Y (2011) Feedback and control of posture and multi-mode coordination in mild cerebellar ataxia. Exp Brain Res 210: 153–163.

43. Knockgether T, Paulson H (2011) Milestones in ataxia. Mov Disord 26: 1134–1141.