

# 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, X25, 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<sup>2</sup> 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, [3] 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 Llagas* Social Center, *Fisiosalud* 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 Llagas* 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 Llagas* 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

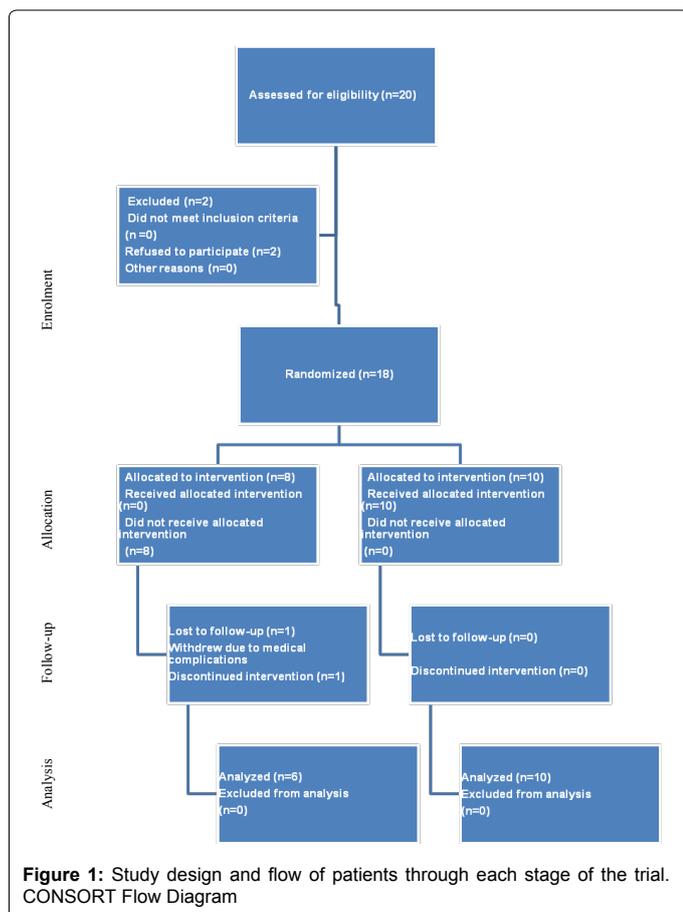
Patients were excluded on the basis of medical records: in addition to meeting the inclusion criteria, it was required that patients had no serious concomitant illnesses, such as active arrhythmia, significant heart failure, or dementia. Failure in a previous physical condition examination, absence from 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*<sup>®</sup>, to one of two treatment groups: the control group ( $n = 6$ ;  $48.17 \pm 3.920$  years old; 3 women; 3 men) received the usual pharmacological treatment, while the intervention group ( $n = 10$ ;  $56.4 \pm 4.061$  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 specialized 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 (Sintrom®) 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
<b>General physical condition (10 minutes)</b>	Reduction of osteomyoarticular retractions. Improve muscle tone. Increase respiratory capacity. Increase 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
<b>Specific physical condition (15 minutes)</b>	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.
<b>Prefunctional training (20 minutes)</b>	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
<b>Functional training (15 minutes)</b>	Consolidate previous achievements. Improve equilibrium, coordination, and rhythm. Improve gait	Coordination training (activities with balls). Motorized movement therapy machine, for lower and upper extremities (artromotor Motormed®).

**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  $P \leq 0.05$  (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  $53.31 \pm 5.654$  years at the start of the study and  $12.33 \pm 1.821$  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).

Characteristic	Control Group (n=6)	Intervention Group (n=10)
<b>Age, years</b>		
Mean (SD)	56.4 (4.061)	48.17(3.920)
Range	48-61	44-55
Female sex, %	40	50
<b>History of the disease (years)</b>		
Mean (SD)	33.8 (2.898)	32.50(2.881)
Range	29-38	26-37
<b>Age at initial diagnosis, years</b>		
Mean (SD)	13.4 (1.838)	11.3(0.816)
Range	10-15	10-12
Mobility indoors, %		
Wheelchair user	100	100
Cardiomyopathy, %		
HCM	70	65
Diabetes Mellitus, %	40	40
Digestive Disorders, %		
Crohn's disease	30	20

a. Demographic and clinical characteristics of patients

Student's t test			
History of FA	32.5 ( $\pm$ 2.881)	33.8( $\pm$ 2.898)	0.399
mean (standard deviation)			

<sup>a</sup> Number of male or female

b. Characteristics of the groups of study. In the first row, Chi-squared test was used to analyze the qualitative variable "sex". In the second row, the quantitative variable "History of Friedreich's Ataxia (FA)" was analyzed with the Student's t-test.

**Table 2:** Characteristics of the groups of study.

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.

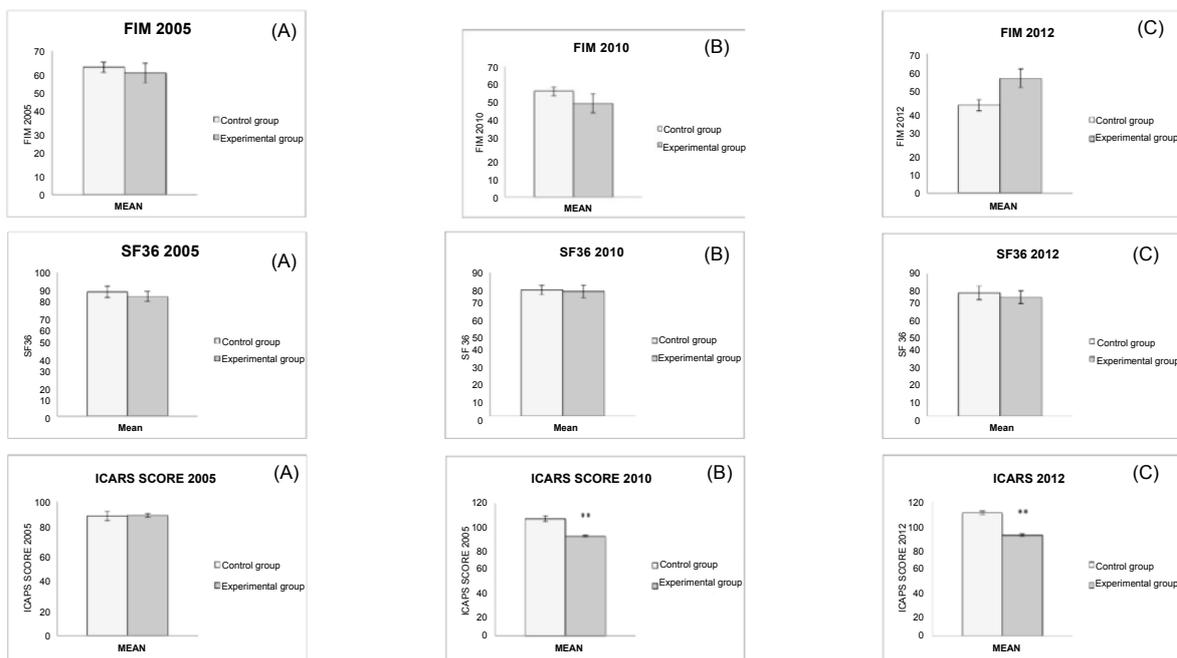
We also calculated the p value for the comparison between the mean scores on the FIM, SF-36 and ICARS, in the three different time points; pre-test; post- test; and at 2 years of follow-up (Figure 3). Among these clinical measures, the mean FIM and SF-36 scores had decreased by the end of the treatment 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  $50.20 \pm 16.02$  to  $59.20 \pm 15.01$ ). 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.

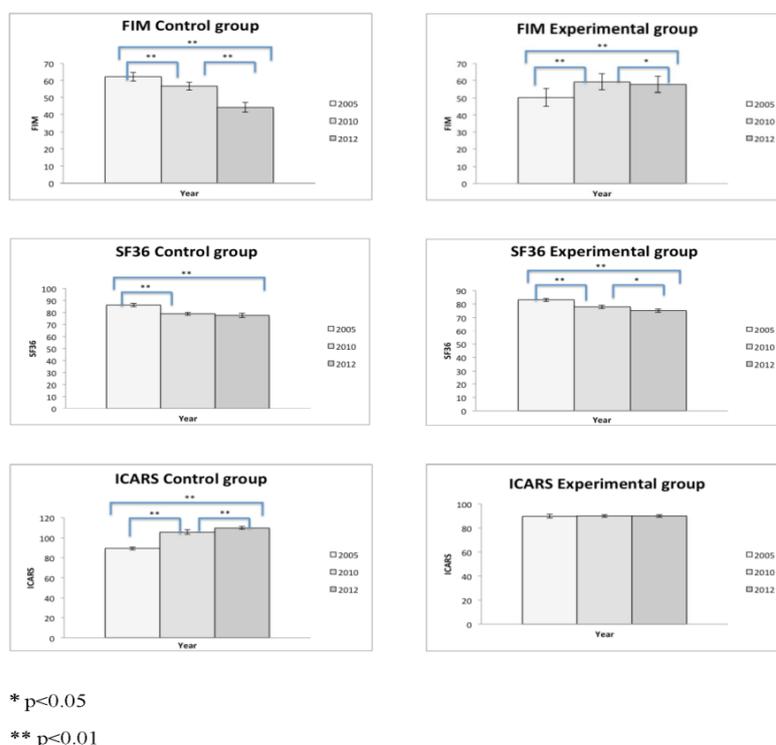
Further, the mean ICARS scores did not vary significantly from the start to the end of the treatment period, remaining similar at the end of the follow-up (Figure 3). This could be interpreted as a plateauing of the degree of dependence of those who received the intervention. Appendix 4 summarizes the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

	ANOVA	pvalue
<b>ICARS score 2005</b>	Control group	0.839
	Interventiongroup	
<b>ICARS score 2010</b>	Control group	0.000**
	Interventiongroup	
<b>ICARS score 2012</b>	Control group	0.000**
	Interventiongroup	
<b>FIM 2005</b>	Control group	0.655
	Interventiongroup	
<b>FIM 2010</b>	Control group	0.362
	Interventiongroup	
<b>FIM 2012</b>	Control group	0.053
	Interventiongroup	
<b>SF36 Healthsurvey, 2005</b>	Control group	0.103
	Interventiongroup	
<b>SF36 Healthsurvey, 2010</b>	Control group	0.604
	Interventiongroup	
<b>SF36 Healthsurvey, 2012</b>	Control group	0.254
	Interventiongroup	

\*\* p<0.01

**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. ANOVA was performed for the three different time points: pre-test, 2005; post-test, 2010; and at 2 years of follow-up.

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 by objective measures and provide a clearer picture of the wider impact of FA. Apart from one previous study that found disability has an influence on work and social activities for people with FA [28], a comprehensive literature search identified no quality of life studies in FA using standardized measures. In relation to this, Wilson et al. [29] analyzed the impact of FA on quality of life, noting that late onset was one of the factors negatively associated with quality of life, but also that there were limitations associated with the use of SF-36<sub>v2</sub> in the FA population [12]. Indeed, Delatycki [30] commented that there is a critical need for accurate measurement tools to detect such subtle benefits but that generic questionnaires, such as the SF-36, may not provide appropriate primary outcome measures in FA clinical trials. In addition, in an open-labelled prospective survey, Ribai et al. [19] examined 104 FA patients every 6 months during a median period of

5 years (range, 6 months to 7 years), with a systematic standardized protocol, and concluded that the neurological condition of FA patients deteriorated slowly over time, and that 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 implemotor 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

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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