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ORIGINAL PAPER

Effects of Physical Rehabilitation in Patients with Spinocerebellar Ataxia Type 7

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Abstract

Today, neurorehabilitation has become in a widely used therapeutic approach in spinocerebellar ataxias; however, there are scarce powerful clinical studies supporting this notion, and these studies require extension to other specific SCA subtypes in order to be able to form conclusions concerning its beneficial effects. Therefore, in this study, we perform for the first time a case-control pilot randomized, single-blinded, cross-sectional, and observational study to evaluate the effects of physical neurorehabilitation on the clinical and biochemical features of patients with spinocerebellar ataxia type 7 (SCA7) in 18 patients diagnosed with SCA7. In agreement with the exercise regimen, the participants were assigned to groups as follows: (a) the intensive training group, (b) the moderate training group, and (c) the non-training group (control group).

We found that both moderate and intensive training groups showed a reduction in SARA scores but not INAS scores, compared with the control group ($p < 0.05$). Furthermore, trained patients exhibited improvement in the SARA sub-scores in stance, gait, dysarthria, dysmetria, and tremor, as compared with the control group ($p < 0.05$). No significant improvements were found in daily living activities, as revealed by Barthel and Lawton scales ($p > 0.05$). Patients under physical training exhibited significantly decreased levels in lipid-damage biomarkers and malondialdehyde, as well as a significant increase in the activity of the antioxidant enzyme PON-1, compared with the control group ($p < 0.05$). Physical exercise improved some cerebellar characteristics and the oxidative state of patients with SCA7, which suggest a beneficial effect on the general health condition of patients.

Keywords Spinocerebellar ataxia type 7 · Physical rehabilitation · Neurorehabilitation · Cerebellar features · Oxidative stress markers

Karla Tercero-Pérez and Hernán Cortés contributed equally to this work.

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Introduction

Spinocerebellar ataxia type 7 (SCA7) is a hereditary neurodegenerative disease caused by an expansion of a cytosine-adenine-guanine (CAG) trinucleotide repeat located in the *ATXN7* gene coding region [1]. This abnormal expansion of CAG repeats elicits the incorporation of a rich polyglutamine tract in ataxin-7 protein, and the negative dominant effect of the mutant protein in turn causes gives rise to the loss of neuron populations, mainly in cerebellum, retina, and brainstem, leading to diverse clinical manifestations, including progressive gait ataxia, pigmental macular dystrophy, dysmetria, dysarthria, dysdiadochokinesia, sensory loss, hyperreflexia, and postural tremor [2, 3].

At present, to our knowledge, there are no available therapies to halt or reverse the SCA7 disease course; thus, current treatments are limited to only managing symptoms. In this scenario, the physical rehabilitation of patients constitutes a feasible alternative approach to improve the quality of life in patients with SCA7 and, possibly, to slow disease progression [4]. Previous studies in patients with neurodegenerative and neuromuscular diseases [5], including Huntington disease [6], and myotonic dystrophy [7], or some indistinct types of cerebellar ataxias [8–16], have demonstrated that the prescription of aerobic exercise and low-to-moderate intensity strength training can help patients to maintain independence in daily living activities. Interestingly, previous studies in patients with SCA2 or SCA3 suggested that physical rehabilitation improved gait and balance [8–12]. However, these studies need to be extended to other specific SCA subtypes in order to be able to arrive at conclusions concerning the beneficial effects of such therapies for treating cerebellar ataxias [15–18]. In particular, physical rehabilitation studies on SCA7 remain to be approached, due mainly to its low frequency worldwide (1/100,000 inhabitants) [17].

In this study, we implemented a 24-week adapted exercise-training program to analyze the effect of physical rehabilitation on SCA7 pathophysiology, analyzing a cohort of clinically and genetically well-characterized patients. The improvement in performance of patients was evaluated using neurological analysis and activities-of-daily-living scales. Furthermore, we evaluated whether the benefit of physical activity is reflected in markers of oxidative stress.

Materials and Methods

Participants

Eighteen patients diagnosed with SCA7 were recruited from the Central region of Veracruz State (Mexico) by the National Rehabilitation Institute-Luis Guillermo Ibarra Ibarra (INR-LGII) and the Rehabilitation and Social Inclusion Center of Veracruz-DIF (CRIS-DIF), between August 2016 and April 2017. The study was approved by the Ethical and Research Committee of the INR-LGII and signed informed consent was obtained from all patients prior to participation. All procedures were carried out according to the Code of Ethics of the Helsinki Declaration. This research is a case-control, cross-sectional, and observationally designed study. Inclusion of patients was based on clinical examination and molecular diagnosis [18]. The study only includes patients with Klockgether clinical stages 1 (fully ambulatory with moderate disability) and 2 (dependence of ambulatory assistance devices) [19]. Patients with other genetic ataxias or non-genetic secondary ataxias were excluded. None of the patients had participated previously in a physical activity therapy.

Interventions

To study the effects of physical rehabilitation on SCA7, we implemented a specific exercise regimen that comprised a 24-week period, on the basis of previous physical rehabilitation studies on SCA2 [9, 10] and the beneficial effects of physical rehabilitation in these patients (Table 1), because SCA2 and SCA7 share a similar disease course and clinical symptomatology. The participants were assigned to each study group as follows: (a) intensive training group. This group received five weekly sessions of 2 h each for a 24-week period. (b) Moderate training group. This group received three weekly sessions of 2 h each for a 24-week period. (c) Control group (the non-training group). This group did not receive any training. Thus, the total number of training sessions was 120 and 72 for the intensive training and moderate training groups, respectively. The patients were first separated into three blocks matched by age, and then, blocks were randomly allocated to the intervention and control groups. Control-group members were subsequently invited to participate in the neurorehabilitation program. Patients in all groups were instructed not to make any changes in their normal daily activities and habits. Training sessions were supervised by a specialist in physical therapy and a specialist in physical medicine and rehabilitation. Global objectives were focused on the maintenance of motor control, coordination exercises, gait re-education, dynamic and static balance, physical conditioning, and muscular strengthening. It is noteworthy that physical activities were adjusted accordingly to the visual status of the patients. Patients with visual impairments were verbally instructed on the physical activity to perform, while patients with blindness were directly assisted by the therapist to perform the exercising and the proprioceptive direction. Therefore, two different routines were established according to the patient's clinical classification (Table 1) [19]. Clinical assessments were performed at three different times: before training (BT), after 12 weeks of training (12WT) and after 24 weeks of training (24WT). Biochemistry measurements and

Table 1 Description of physical training

Time	Activities for patients of stage 1
10 min	PresentationBreathing exercises and relaxation techniques Stretching routine for muscle groups in upper and lower extremities
20 min	Active movements at 4 limbs against gravity
	Individual calisthenics routine without progressive resistance
40 min	Physical conditioning - Strengthening to upper and lower extremities with progressive resistance - Work group or in pairs - Coordination activities for upper and lower extremities
10 min	Break and hydration
20 min	Balance and gait- Static standing balance - Static balance with feet together and hold - Alternating legs trying to keep standing balance - Walking on flat ground with reinforcement in phases of gait - Gait - Walking on uneven ground - Walking dodging objects
10 min	Recovery and relaxation
Time	Activities for patients of stage 2
10 min	Presentation Breathing exercises and relaxation techniques Stretching routine for muscle groups in upper and lower extremities in preparation for exercise
15 min	Active movements at 4 limbs against gravity
	Individual calisthenics routine without progressive resistance or use of bike or stair climber
40 min	Physical conditioning: - Strengthening to upper and lower extremities with progressive resistance in parallel bars or with the assistance of relative/volunteer - Squats with support guardrail or assistance - Leisure activities of motor coordination of upper and lower extremity using rings, balls and cane.
15 min	Break and hydration
20 min	Motor control: - Balance in standing decreasing support base with support bars or guardrail - Balance in standing with feet together with support bar or guardrail, trying to reduce assistance or support to hold the position. - Alternating legs with support, stimulating standing balance - Up and down stairs with support - Walking on flat ground with support guardrail or family/volunteer, with emphasis on phases of gait, reinforcing auditory feedback.
10 min	Recovery and relaxation

evaluations of the patients' performance in activities of daily living were carried out at BT and 24WT.

Outcome Measurements

A comprehensive neurological evaluation of the patients was carried out following Mayo Clinic procedures [20]. Severity of cerebellar features was assessed using the Scale for Assessment and Rating of Ataxia (SARA) [21], while assessment for extracerebellar symptoms was evaluated utilizing the Inventory of Non-Ataxia Symptoms scale (INAS) [22]. Disease age at onset was determined by the presence of the first motor or visual symptom. Evaluation of performance in daily-living activities was conducted using the Lawton and Barthel scales, as previously described [23]. For evaluation of oxidative stress markers, blood samples were collected into EDTA and heparin-treated tubes (BD Vacutainer, USA). Samples were then processed to obtain plasma and erythrocyte lysates and further stored at − 70 °C until their analysis. Biochemical tests were carried out as previously described [24]. Protein damage was analyzed by quantification of dityrosines (DT) levels, while protein carbonylation was measured by the treatment of plasma samples with 2, 4-dinitrophenylhydrazine (DNPH). Lipid oxidation was assayed

by quantification of lipid hydroperoxides (LHP) and malondialdehyde (MDA) in plasma. Antioxidant defense was analyzed through the activity of glutathione reductase (GR) and glutathione peroxidase (GPx) enzymes, measuring the rate of NADPH oxidation in erythrocyte lysates. Paraoxonase (PON-I) activity was determined by the hydrolysis of diethyl p-nitrophenyl phosphate (paraoxon) in plasma.

Statistical Analysis

For descriptive statistics of continuous variables, means and standard deviations (SD) were calculated, while categorical variables were expressed as proportions. Kolmogorov-Smirnov test was employed to assess normality of variables. Differences in age, age-at-onset, disease time span, and CAG repeats were analyzed by Kruskal-Wallis test. The effects of physical training on SARA, INAS, and the Lawton and Barthel scales were assessed by a two-way, repeated-measure analysis of variance (ANOVA), followed by a post hoc Newman-Keuls test. Differences in the levels of oxidative stress markers were determined by Wilcoxon signed-rank test. P values < 0.05 were considered significant. All data were analyzed using Prism version 6.01 statistical software (Graph Pad Software, San Diego, CA, USA).

Results

Effect of Physical Training on SCA7 Neurological Features

A total of 18 SCA7-affected individuals (13 males and 5 females) ranging in age from 17 to 64 years (mean, 39.94 years; standard deviation [SD], 15.57 years) were separated into three different groups (non-training, moderate training, and intensive training). The demographic features of patients belonging to each experimental group are described in Table 2; no significant differences in the demographic characteristics were found between the experimental groups. Physical exercise was generally well tolerated and there were no harmful events associated with it; moreover, the retention rate was 100% in both intervention groups. The effect of physical training on cerebellar and non-cerebellar symptoms was evaluated by SARA and INAS, respectively. Interestingly, a slight but significant reduction of cerebellar symptoms (SARA score; $p < 0.05$) was observed in the moderate and intensive training groups (0.5 and 1.4, respectively) after 12 and 24 weeks of intervention, compared with the non-training group, which demonstrated an increase of 1 point on average (Fig. 1a). Consistently, the proportion of patients who exhibited decreased SARA scores increased up to 50% and 60% in the moderate and intensive training groups, respectively, vs. 14% in the control group. Likewise, the proportion of patients showing increased SARA scores was considerably higher in the control group (70%) compared to the moderate (33%) and intensive training (40%) groups, suggesting a positive correlation between the decrease of disease severity and the physical rehabilitation therapy (Fig. 1b). In order to analyze this beneficial effect more in depth, cerebellar features were analyzed separately. A substantial improvement in gait, sitting, dysarthria, dysmetria, and tremor and a mild improvement in stance were observed in both the moderate and intensive training groups, compared with the control group (Fig. 1c). In contrast, no difference was observed between control and physically trained patients in terms of extracerebellar features (Supplemental Fig. 1). However, no statistically significant differences were found between moderate and intensive training groups.

Table 2 Demographic characteristics of SCA7 patients

General features	Control group ($n = 7$)	Moderate training group ($n = 6$)	Intensive training group ($n = 5$)	P
Population characteristics				
Age (mean ± SD years)	39.71 ± 18.17	41.33 ± 16.17	38.60 ± 14.22	0.986
Age at onset	26.43 ± 12.66	29.50 ± 8.5	31.60 ± 13.46	0.782
Disease time span	13.29 ± 9.65	11.83 ± 10.70	8.75 ± 2.73	0.722
Molecular analysis				
CAG repeats	47.71 ± 5.88	46.33 ± 4.97	46.00 ± 5.19	0.886
Neurological rating scales				
SARA	15.64 ± 5.33	18.58 ± 3.64	16.40 ± 6.39	0.538
INAS	4.14 ± 2.19	3.89 ± 0.41	3.40 ± 0.89	0.365

SD standard deviation, *CAG* cytosine-adenine-guanine, *SARA* Scale for Assessment and Rating of Ataxia, *INAS* inventory of non-ataxia symptoms

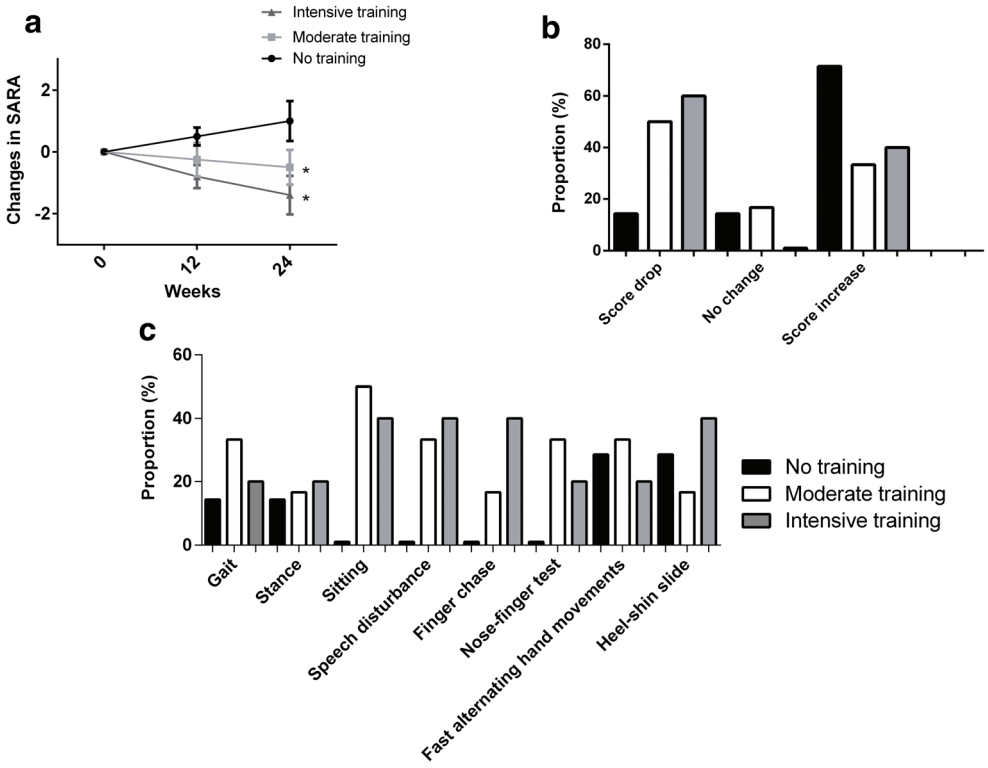

Fig. 1 Effect of physical training on cerebellar features of patients with SCA7. **a** Patients subjected to no training (black circle plot), moderate training (gray square plot), or intensive training (gray triangle plot) were evaluated by the SARA score at baseline, at 12 weeks, and at 24 weeks of treatment. Asterisks denoted significant differences. **b** The percentage of patients from each experimental group showing an increase, a decrease, or no change in SARA values after 24 weeks of treatment is shown. **c** Comparison of the percentage of subjects who exhibit drops in SARA subscores. **b**, **c** Black, white, and gray columns represent the no training, moderate training, and intensive training groups, respectively

Effect of Physical Training on Daily-Living Activities

To provide insight into the effect of physical training on performance of activities of daily living, we used the Barthel Index of Activities of Daily Living and the Lawton Instrumental Activities of Daily Living Scale. During the clinical interview, the majority of the patients subjected to training referred improvement in their performance of daily activities (83.33% and 80% for the moderate and intensive training groups, respectively, vs. 14.28% for the non-training patients); on contrast, no significant differences were found among the groups upon employing Barthel and Lawton scales (Fig. 2a, b). However, the moderate training group revealed a strong tendency toward an increase in the Lawton scale score, suggesting a possible improvement in the specific activities measured by this scale.

Effect of Physical Training on Oxidative Stress Markers

To ascertain whether physical therapy exerts an effect on the oxidative state of patients with SCA7, different circulating biomarkers of oxidative stress were assessed before and after physical intervention (24 weeks of training). With respect to protein damage, no differences were observed in the content of protein carbonylation (DNHP levels) among the three experimental groups, neither before nor after exercise training (Fig. 3a). Conversely, a significant decrease in dityrosine (DT) levels was found for all of the experimental groups after intervention (Fig. 3b), suggesting that the protein damage exhibited by patients with SCA7 decreased over time, regardless of the rehabilitation program. Interestingly, physical training resulted in significantly decreased levels of lipid damage

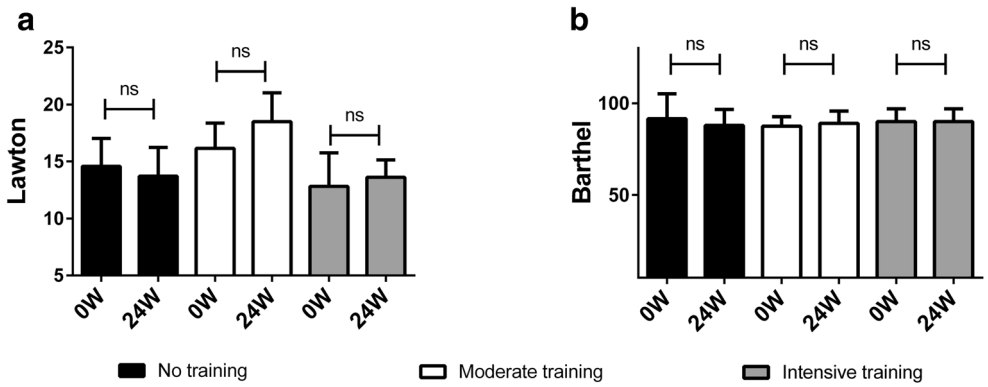

Fig. 2 Performance of daily living activity scales in patients with SCA7 before and after physical training. Patients subjected to no training (black columns), moderate training (white columns), or intensive training (gray columns) were evaluated by Lawton (A)- and Barthel (B)-value scores at baseline, at 12 weeks, and at 24 weeks of treatment

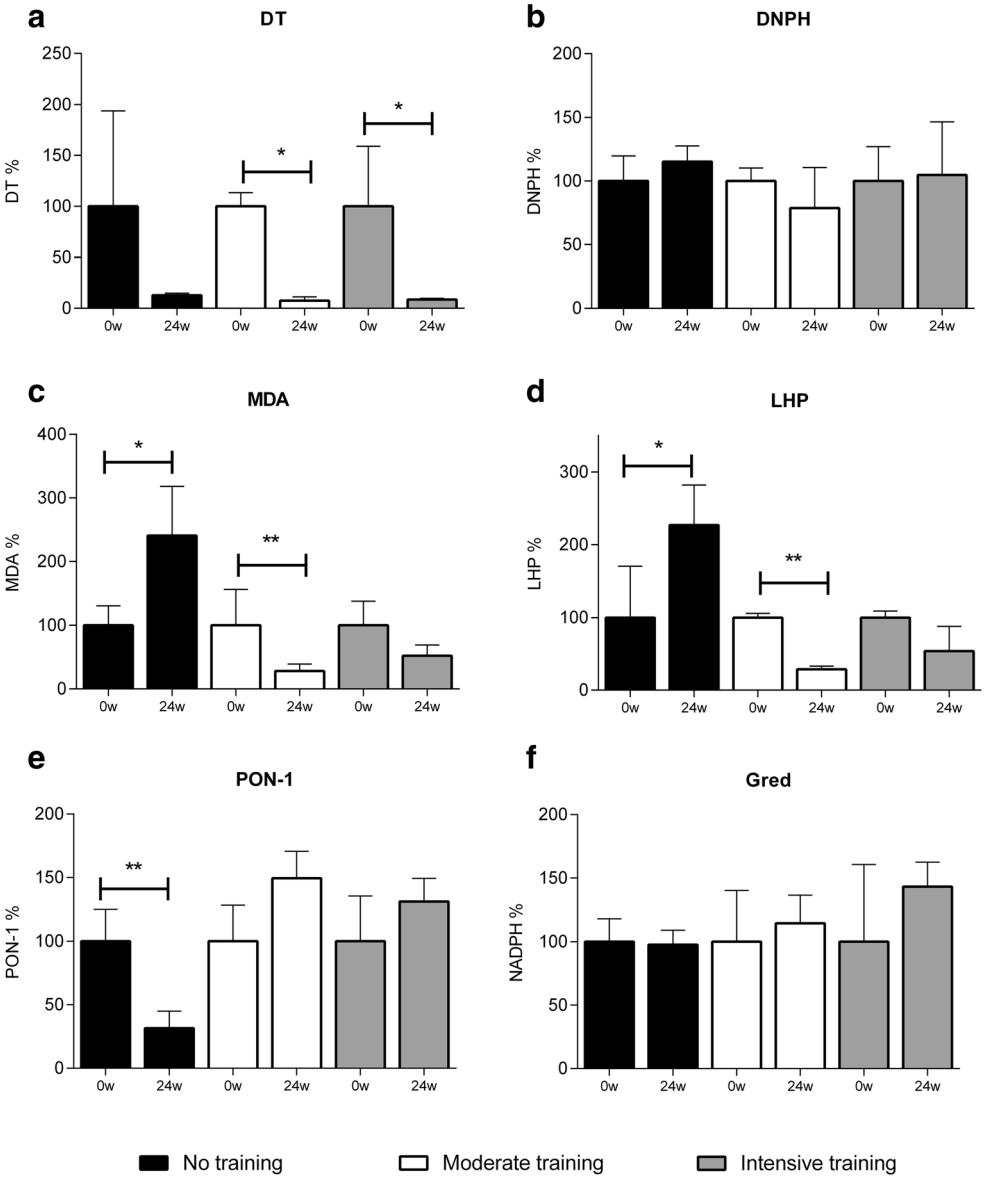

Fig. 3 Effects of the neurorehabilitation training on oxidative stress markers in patients with SCA7. Markers of damage to proteins: **a** dityrosines [DT] and **b** protein carbonylated [DNPH]; markers of damage to lipids: **c** malondialdehyde [MDA] and **d** lipohydroperoxides [LPH]. The antioxidant defense enzymes evaluated were the following: **e** paraoxonase-1 [PON-1] and **f** cupric ion reducing capacity [Gred]. Assessments were performed at baseline and at 24 weeks of treatment in all analyzed groups

markers in the two rehabilitation groups (Fig. 3c, d) we found, in the moderate training group, decreases of 72% and 47% for MDA and LPH, respectively, whereas the intensive training group exhibited decreases of 70% and 42% for the same lipid damage parameters. It is noteworthy that the non-training control group exhibited increased values in both parameters (MDA and LPH). Since the non-training group showed increased MDA and LPH values over time, it appears that the rehabilitation program effectively prevented such lipid damage. With respect to the antioxidant defense system, PON-1 activity markedly diminished over time in the non-training patients, while the trained patients demonstrated no decline, but even a slight increase of this enzymatic activity, after rehabilitation (Fig. 3e), implying that exercise training maintained and even improved the antioxidant response in patients with SCA7. However, it is worth to mention that no statistically significant differences were found between moderate and intensive training groups. Finally, no difference was observed in NADPH levels among the three experimental groups (Fig. 3f), neither before nor after physical intervention, suggesting no effect of physical exercise on the activity of GR and GPx enzymes.

Discussion

Few studies have evaluated the effects of physical therapy on diverse motor features and functional performance in patients with cerebellar ataxias; furthermore, the evaluation of patients in these studies was carried out without distinction of the type of ataxia [11–14, 25]. Since clinical and molecular features

vary among SCA sub-types, it is necessary to analyze the effect of physical rehabilitation on each particular ataxia.

In this study, we reported, to our knowledge for the first time, the therapeutic effect of exercise training on patients with SCA7. Interestingly, we showed that moderate and intensive training improved cerebellar features in the majority of patients, as measured by SARA. Some inter-patient variability was observed, most likely due to differences in age, duration of illness, disease stage, and the patient's motivation; however, no statistically significant differences were found between the experimental groups for these demographic characteristics. Separate analysis of SARA sub-scores revealed improvement in sitting, gait, dysarthria, dysmetria, stance, and tremor items. It is tempting to speculate that improvement in sitting, stance, and gait is associated with increased physical strength, while improvement in dysarthria and dysmetria might indicate the amelioration of cerebellar symptoms. Consistent with this notion, Burciu et al. reported that the sensorimotor training of patients with cerebellar ataxias produced an increase in cerebellum volume, mainly in neocortical areas of the cerebellar-cortical loop [26]. Thus, we hypothesized that physical training can induce cerebellar plasticity in the patient's remaining healthy tissue; supporting this hypothesis, elevated brain-derived neurotrophic factor (BDNF) levels were found in cerebellum, motor cortex, and hippocampus, in response to physical exercise [27–29]. BDNF plays a role in diverse neuronal processes, including neuronal survival, synaptic plasticity, and Purkinje cell differentiation. Further studies to assess the expression of BDNF and/or other neurotrophins in patients with SCA7 upon physical rehabilitation are required to approach this hypothesis. Conversely, physical therapy did not appear to improve non-cerebellar symptoms, as measured by INAS. In contrast with the discrepancy in our findings, Burciu et al. reported increases in the brain areas of ataxic patients after sensorimotor training [26]. Such inconsistency between the two studies might depend on differences in the training program and/or the duration of exercise intervention, or could suggest that exercise did not significantly influence specific brain areas, possibly areas that were more affected by the disease, that participate in items measured by INAS.

Although the self-perception of patients referred improvement in their activities of daily living, particularly in balance and strength, assessment by the Lawton and Barthel scales failed to confirm any significant enhancement. A possible explanation is that these scales were designed to evaluate geriatric individuals; thus, alternative tools aimed to specifically assess ataxic patients are needed to clarify this point.

Finally, owing to the contribution of oxidative stress to pathogenesis of SCA7 [24, 30], we were prompted to analyze whether exercise therapy is reflected in the oxidative state of patients. Interestingly, decreased levels of lipid damage markers (MDA and LHP) were found in trained patients, concomitantly with the increased activity of the antioxidant enzymes PON-1. Recent studies suggested that exercise-mediated induction of reactive oxygen species (ROS) and LHP is modulated by the antioxidant defense, which is in agreement with our results; the positive modulation of PON-1 observed in the trained groups could in turn alter the metabolic pathways of lipid peroxidation, leading to the depletion of MDA and LHP levels. Consistent with these findings, Rodríguez et al. observed increased glutathione S-transferase (GST) activity upon physical rehabilitation of patients with SCA2, while Cui et al. reported reduced cerebellar oxidative damage in rodents subjected to physical exercise [9, 31]. With respect to protein damage, we were unable to observe perceptible improvements. We found decreased DT levels for all experimental groups, suggesting oxidative protein damage associated with the disease progression; however, no differences were observed in DNHP levels in response to physical exercising. This discrepancy could be explained, at least in part, as due to that the DNHP is produced by different chemical modifications other than DT, such as the breaking of hydrogen bonds in the secondary structure of the protein or by the formation of adducts with MDA, which might be refractory to excercise [32, 33].

Taken together, these data suggest that physical therapy counteracts the oxidative damage in patients with SCA7 through the prevention of lipid damage and induction of the anti-oxidant system. Therefore, evaluation of oxidative stress biomarkers suggests the usefulness of predicting the disease course and of evaluating therapeutic interventions, as has been observed in several neurodegenerative diseases, such as Parkinson disease, Alzheimer disease, and SCA2 [34–36]. However, no differences were observed between the intervention groups, which suggests that further improvements from moderate to intensive training were difficult to achieve, due likely to a ceiling effect, because mechanisms of neuroplasticity are not unlimited [37]. Additional studies will help to determine the optimal frequency and duration of physical activity required for clinical benefits. The main limitation of this study was the relatively small sample size analyzed. Nevertheless, the cohort of 18 patients was highly valuable because of the rare incidence of SCA7. Another limitation comprised that the SCA7 of all patients studied derived from a founder mutation; thus, further analyses comparing patients from different populations are required to sustain the beneficial effect of physical training on SCA7. Finally, larger longitudinal studies are required to ascertain whether cerebellar and stress oxidative improvements are maintained at the long term.

Conclusions

We provide evidence showing that physical intervention ameliorated several cerebellar manifestations and improved the redox state of patients with SCA7, supporting the notion that

physical training could positively influence their general health condition.

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Compliance with Ethical Standards

The study was approved by the Ethical and Research Committee of the INR-LGII and signed informed consent was obtained from all patients prior to participation. All procedures were carried out according to the Code of Ethics of the Helsinki Declaration.

Informed Consent An informed consent form was signed by all subjects prior to examination and the research protocol was approved by the National Rehabilitation Institute (INR, Mexico City) Research and Ethical Committee.

Conflicts of Interest The authors declare that they have no conflicts of interest.

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