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RESEARCH REPORT

Balance exercise in patients with chronic sensory ataxic neuropathy: a pilot study

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Abstract Although exercise therapy is considered part of the treatment of neuropathic patients, and somatosensory input is essential for motor learning, performance and neural plasticity, rehabilitation of patients with sensory ataxia has received little attention so far. The aim of this prospective pilot study was to explore the short- and medium-term efficacy of a 3-week intensive balance and treadmill exercise program in chronic ataxic neuropathy patients; 20 consecutive patients with leg overall disability sum score (ODSS-leg) ≥2, absent/mild motor signs, clinical and therapeutic stability ≥4 months were enrolled. Evaluations were done at baseline, at the end of treatment and at 3- and 6-month follow-up. Outcome measurements included: ODSS-leg, Berg balance scale, 6-min walk distance, and the functional independence measure (FIM) scale. The short-form-36 health status scale (SF-36) was used to measure health-related quality of life (HRQoL). ODSS-leg improved significantly compared with baseline, 3 weeks, 3 months (primary outcome), and 6 months follow-up. A significant improvement in all functional secondary outcome measurements and in some SF-36 subscales was also observed. This pilot study suggests that balance exercise is safe and well tolerated and might be effective in ameliorating disability and HRQoL in patients with chronic peripheral sensory ataxia.

Key words: balance, exercise therapy, gait disorders, polyneuropathy, sensory ataxia

Introduction

Peripheral neuropathies are a wide range of diseases affecting the peripheral nerves, whose estimated prevalence is 2%–3% in the general population and as high as 8% in people over the age of 55 years *(England and Asbury, 2004)*. Functional impairment may contribute to persistent disability and reduced autonomy, which might in turn lead to obesity, increased risk of cardiovascular disease, and reduced health-related quality of life (HRQoL) *(McDonald, 2002; Graham et al., 2007; van Schie, 2008)*. While exercise therapy is considered to be part of the treatment for people with peripheral neuropathy *(Hughes et al., 2006)*, few studies have evaluated the effect of exercise on functional recovery in patients affected by sensory–motor neuropathies *(Lindeman et al., 1995; Ruhland and Shields, 1997; Richardson et al., 2001)*. Furthermore, despite the fact that somatosensory input is essential for accurate motor performance *(Pearson, 2000)*, learning new motor skills *(Pavlides et al., 1993)* and neural plasticity and recovery after injury *(Krivanekova et al., 2011)*, there has been only one study focusing on the short-term effect of a balance rehabilitation program in peripheral neuropathy

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and multiple sclerosis patients with sensory ataxia *(Missaoui and Thoumie, 2009)*. Hence, the aim of this prospective, single centre pilot study was to explore the short- and medium-term clinical effect of an intensive exercise program in a group of patients exhibiting chronic peripheral sensory ataxia, which represents a relatively rare subgroup of patients within the spectrum of peripheral neuropathies *(Sheikh and Amato, 2010)*.

Materials and Methods

Subjects

Twenty consecutive patients with a clinical diagnosis of chronic sensory ataxia caused by peripheral nervous system disease of any etiology were included in this study (Fig. S1, Supporting information). Patients provided informed consent to the study, approved by the local ethic committee. Inclusion and exclusion criteria were:

- Age 18–80 years old.
- Sensory symptoms and signs predominant over motor symptoms and signs. Patients should be strong enough to stand on their heels and toes, and have leg muscles Medical Research Council (MRC) strength grade ≥4.
- No change in self reported disability or medication in the previous 4 months.
- Electrodiagnostic tests consistent with a diagnosis of chronic peripheral neuropathy/sensory neuronopathy *(Kimura, 1993; Camdessanche et al., 2009)*. Patients exhibiting signs of active denervation at electromyography were excluded.
- Leg overall disability sum score (ODSS-leg) subscale ≥2.
- Patients who had not already performed within 12 months before screening or were not already regularly performing an exercise therapy program.
- Patients presenting any other neurological, musculoskeletal, or medical disorders that would influence outcome-measure scoring were excluded.

Therapy exercises

The exercise therapy was performed in the hospital gymnasium. Each patient underwent 30 sessions, 2 sessions daily (morning and afternoon) for five consecutive days. Each patient's treatment lasted three consecutive weeks (weekend excluded). All components of the exercise session were prescribed by a physiotherapist, ensuring that participants could perform each exercise effectively and safely. The morning session was specifically devoted to balance training. Each exercise session was individually tailored and designed to take approximately 1 h. Static and dynamic exercises were considered under different conditions, the complexity of the task progressively increasing: bipedal, tandem, and unipedal stance; eyes open/closed; stable and unstable surfaces; stepping forward and sideways; with or without obstacles. The afternoon session was devoted to treadmill training: walking sessions lasted 20 min of exercise (gradually increased to 30 min, from session to session, if possible) plus 10 min of warm up and warm down. Walking speed, treadmill incline, and upper limb support were individually tailored.

Assessments

Patient evaluations were performed at the start of the study period (baseline), at 3 weeks (end of treatment), and at 3- and 6-month of follow-up. Disability, or activity limitation, was measured using the ODSS *(Merkies et al., 2002a; Merkies and Schmitz, 2006)*. As rehabilitation treatment was focused on balance and walking exercises, ODSS-leg and ODSS-arm subscales were considered separately. The primary outcome was the improvement in ODSS-leg at 3-month follow-up (range: 0–7).

Other secondary outcome measurements included the Berg balance scale *(Berg et al., 1992)*, the 6-min walk distance *(Enright, 2003)*, and the functional independence measure (FIM) *(Dodds et al., 1993)* scales. Muscle strength was evaluated with the MRC sum score (12 muscles) *(Muley et al., 2008)*, while sensory impairment was monitored with the inflammatory neuropathy cause and treatment group (INCAT) sensory sum score (ISS) *(Merkies et al., 2000)*. The self-administered Medical Outcome Study 36-item short-form health status scale (SF-36) was used to measure HRQoL *(Merkies et al., 2002b)*. The 36 items were aggregated to score the eight scales and in turn to calculate the physical component summary score (PCS) and the mental component summary score (MCS) *(Ware et al., 2000; Padua et al., 2005)*. Two independent evaluators, blinded for treatment allocation and for any other ratings, took all the measurements: a neurologist rated ODSS, MRC sum score, and ISS sensory sum score, while a physiotherapist rated Berg balance scale, 6-min walk distance and FIM. Patients were kept blinded for the results of earlier evaluations and unaware of the study hypothesis.

Statistical analysis

For sample size calculation, being ODSS = ODSS-leg + ODSS-arm, we assumed the ODSS-leg standard deviation (SD) less than or equal to ODSS SD and considered, based on historical data on ODSS, a SD of 0.84 for our primary end-point, ODSS-leg *(Merkies et al., 2002a; Kuitwaard et al., 2010)*. To

Table 1. Efficacy of exercise in sensory ataxic patients.

Variable	Baseline (N = 20) Mean (SD)	3 weeks (N = 20) Mean (SD)	3 months (N = 20) Mean (SD)	6 months (N = 19) Mean (SD)
ODSS-leg [median, IQR]	2.7 (0.7) [3, 1]	1.9 (0.6)*** [2, 1]	**2.0 (0.8)** ** **[2, 2]**	1.9 (0.7)** [2,1]
ODSS-arm [median, IQR]	1.6 (0.9) [2, 1]	1.5 (0.8) [2, 1]	1.6 (0.9) [2, 1]	1.5 (0.8) [2, 1]
BBS	40.1 (12.3)	47.4 (10.4)***	46.5 (10.7)***	44.7 (10.7)*
6MWD	279.7 (112.4)	335.2 (98.9)**	323.9 (111.8)*	322.2 (96.6)*
FIM	112.3 (8.6)	116.5 (7.1)**	119.0 (5.8)**	118.7 (6.1)**
MRCss	95.6 (5.5)	96.1 (5.3)	95.4 (5.8)	95.5 (5.7)
ISS	8.9 (4.2)	8.9 (4.2)	9.0 (4.3)	9.1 (4.5)
SF-36				
PCS	33.0 (6.1)	35.7 (7.8)	36.2 (8.4)*	34.0 (7.6)
MCS	41.1 (11.6)	46.4 (11.4)	44.8 (12.1)	42.3 (12.3)
PF	40.3 (19.8)	51.5 (20.0)*	49.5 (21.1)	43.1 (21.4)
RP	13.8 (28.6)	27.5 (37.1)	35.0 (39.2)*	25.0 (34.4)
SF	52.5 (26.5)	63.1 (27.0)*	63.1 (25.5)*	54.4 (25.4)

arm, arm disability scale (range 0–5) (higher values indicate more limitations); ANOVA, analysis of variance; BBS, Berg balance scale (range: 0–56) (higher scores indicate greater independence); FIM, functional independence measure (range: 18–126) (higher values indicate greater independence); IQR, interquartile range; ISS, INCAT sensory sum score (range 0–20) (higher scores indicate more sensory deficits); leg, leg disability scale (range: 0–7); 6MWD, 6-min walk distance (m); MCS, mental component summary; MRCss, Medical Research Council sum score (range 0–100) (higher sum score values indicate better muscle strength); ODSS, overall disability sum score; PCS, physical component summary; PF, physical functioning; RP, role functioning-physical; SD, standard deviation; SF, social functioning, (range 0–100) (higher scores indicate better health); SF-36, Medical Outcome Study 36-item short-form health status scale. Bold: primary outcome.
*$p < 0.05$.
**$p < 0.005$.
***$p < 0.0005$ vs. baseline examination after repeated measure ANOVA (or Friedman test), followed by Bonferroni (or Wilcoxon) *post hoc* tests. ODSS-leg: $\chi^2_{(3)} = 36.11$, $p < 0.0001$; BBS: $\chi^2_{(3)} = 27.03$, $p < 0.0001$; 6MWD: $F(3, 57) = 5.855$, $p = 0.0052$; FIM: $\chi^2_{(3)} = 20.78$, $p = 0.0001$; PCS: $F(3, 57) = 2.854$, $p = 0.045$; PF: $F(3, 57) = 4.272$, $p = 0.0086$; RP: $\chi^2_{(3)} = 7.95$, $p = 0.0469$; SF: $\chi^2_{(3)} = 8.63$, $p = 0.0346$.

detect a change >1 point in ODSS-leg, a sample of 18 patients was required to provide a 95% statistical power ($\alpha = 0.05$). To allow for a dropout rate of 10%, we aimed to enroll 20 patients. The data of all the patients included in the study were considered for efficacy evaluation; a last-observation carried forward approach was used, if required. All results are presented as mean ± SD or median (range), unless otherwise stated. For continuous and normally distributed (as assessed with the Kolmogorov–Smirnov test) variables, results after intervention were analysed using repeated measures analysis of variance (ANOVA) to determine differences among the four evaluation times (baseline, 3 weeks, 3 months, and 6 months). When the sphericity assumption, verified using the Mauchly's criterion, was rejected, the Greenhouse–Geisser correction was applied. *Post hoc* analysis was carried out using the Bonferroni test, in order to detect significant changes compared with baseline examination. For the other variables, results after intervention were analysed using non-parametric repeated measures ANOVA (Friedman test), followed by Wilcoxon signed-rank *post hoc* test, as appropriate. Confidence limits (95%) of the mean or median changes between baseline and time of observation were calculated. Statistical significance was considered at $p < 0.05$. All statistical tests were performed using SPSS software (Technologies, Inc., Chicago, IL, USA).

Results

Patients

About 350 patients have been screened. Baseline characteristics of patients are shown in Table 1. The etiologic diagnosis of the patients included was as follows: idiopathic neuropathy (N = 7); neuropathy associated with anti-myelin-associated glycoprotein antibodies (N = 5); alcohol/nutritional deficiency (N = 3); chronic inflammatory demyelinating polyneuropathy (CIDP, N = 2); stable residual functional impairment after acute inflammatory demyelinating polyneuropathy (disease stability: 20 months, N = 1); neuropathy associated with rheumatoid arthritis (N = 1); and neuropathy associated with chronic hepatitis C virus infection (N = 1). All of the 20 patients completed the entire rehabilitation program; two patients affected by CIDP relapsed in the period between 3- and 6-month follow-ups and were treated with intravenous immunoglobulin therapy. One of these patients was lost at the 6-month follow-up. The exercise therapy resulted safe and well tolerated for all training group patients.

Improvement in activity and impairment measures

Outcome measure results are shown in Table 1. After exercise patients showed a significant

change – over time – in ODSS-leg, Berg balance scale, 6-min walk distance, and FIM scores (Fig. 1).

The median ODSS-leg value was 3 (interquartile range [IQR]: 1, mean: 2.7) at baseline (3 = usually uses unilateral support to walk 10 m), improving to a median value of 2 (IQR: 1) (2 = walks independently but gait looks abnormal) at 3 weeks ($p < 0.0001$), 3-month (primary outcome; $p = 0.001$) and 6-month follow-up ($p = 0.001$) (mean ODSS-leg values: 1.9, 2.0, and 1.9, respectively) *(Merkies et al., 2002a)*. The mean improvement for ODSS-leg at 3 months was −0.62 (95% confidence interval [CI]: −0.83 to −0.41) (Fig. 1A, Table S1).

Secondary outcome measures analysis showed a significant improvement compared with baseline for Berg balance scale, 6-min walk distance and FIM at 3 weeks ($p = 0.0001$, 0.0030, and 0.0008, respectively), at 3-month ($p = 0.0004$, 0.0084, and 0.0020, respectively) and at 6-month follow-up ($p = 0.020$, 0.014, and 0.0045, respectively) (Figs. 1B–D). The mean Berg balance scale value at baseline was 40.1 (SD = 12.3), improving to 46.5 (SD = 10.7) at 3-month follow-up (mean improvement: 6.4; 95% CI: 3.3–9.5). The mean 6-min walk distance at baseline was 279.7 m (SD = 112.4) improving to 323.9 m (SD = 111.8) at 3-month follow-up (mean improvement: 44.2 m; 95% CI: 19.2–69.3). The mean FIM value at baseline was 112.3 (SD = 8.6), improving to 119.0 (SD = 5.8) at 3-month follow-up (mean improvement: 6.7; 95% CI: 3.2–10.1).

No significant changes over time were found for ODSS-arm and for both the impairment measurements MRC sum score and ISS sensory sum score.

Improvement in HRQoL measurements

Changes in patients' HRQoL measurements for each scale of the SF-36 are shown in Table 1. After exercise, a general increase in HRQoL was observed (Fig. 2). A significant change over time was observed for the summary measure PCS, the physical functioning (PF), the role functioning-physical (RF), and the social functioning (SF) scales. Compared with baseline, for the PCS summary score the improvement was significant at 3-month follow-up ($p = 0.023$); for the PF scale the improvement was significant at 3-week follow-up ($p = 0.0016$); for the role functioning-physical scale (RP) the improvement reached statistical significance at 3-month follow-up ($p = 0.026$), while for the social functioning (SF) the improvement was significant at 3-week ($p = 0.038$) and at 3-month follow-up ($p = 0.015$).

Discussion

This pilot study showed that a 3-week intensive balance and treadmill exercise program is safe and well tolerated and suggests potential efficacy in ameliorating disability and functioning in a group of patients affected by disabling, chronic peripheral sensory ataxia. Although some studies demonstrated the effectiveness of exercise therapy in subgroups of sensory–motor neuropathies *(Lindeman et al., 1995; Ruhland and Shields, 1997; Richardson et al., 2001; Graham et al., 2007)*, or in subjects with type-2 diabetes mellitus *(Allet et al., 2010a; 2010b)*, here patients with sensory ataxia were specifically selected. Only one recent study has demonstrated efficacy of balance rehabilitation, immediately after intervention, in a group of ataxic patients with both neuropathy and multiple sclerosis *(Missaoui and Thoumie, 2009)*. After exercise, the disability measurement ODSS-leg improved significantly, not only at the end of the intervention period, but at 3-month (primary outcome) and 6-month follow-up. The median ODSS-leg value improved from 3 to 2, which corresponds to going from using a device for unilateral support to not using a device. Although this could have been due to encouragement by therapists or initial over-reliance on devices, a consistent improvement of balance, as measured by the Berg balance scale, of walking speed, as measured by the 6-min walk distance, and of the functional scale FIM was also observed, thus making this single hypothesis unsatisfactory. On the contrary, no significant improvement in arm disability (ODSS-arm) was observed. This finding indirectly confirms the specific efficacy of the exercise program, as no upper-limb exercise regimen was performed. Moreover, measurements of motor and sensory impairment did not change over time, thus making the hypothesis that the improvements might be secondary to an intrinsic amelioration of the neuropathy unlikely. As somatosensory input is essential for neural plasticity and recovery after injury *(Krivanekova et al., 2011)*, the explanation of the results of our study are not obvious. Possible interpretations of the functional recovery might be enhanced vestibular or visual system balance control compensation *(Diener and Dichgans, 1988; Stenneken et al., 2006)*, reconditioning, or increased capacity of patients to anticipate balance perturbations *(Horak and Hlavacka, 2001; Nardone et al., 2010)*, even though we cannot exclude the effect of proprioceptive stimulation of more proximal limb segments. Although improvement remained significant till 6-month follow-up, some treatment benefit was lost over time. This might be due to not only the natural history of the underlying neurological disease, but also to the limits of the intervention exercise

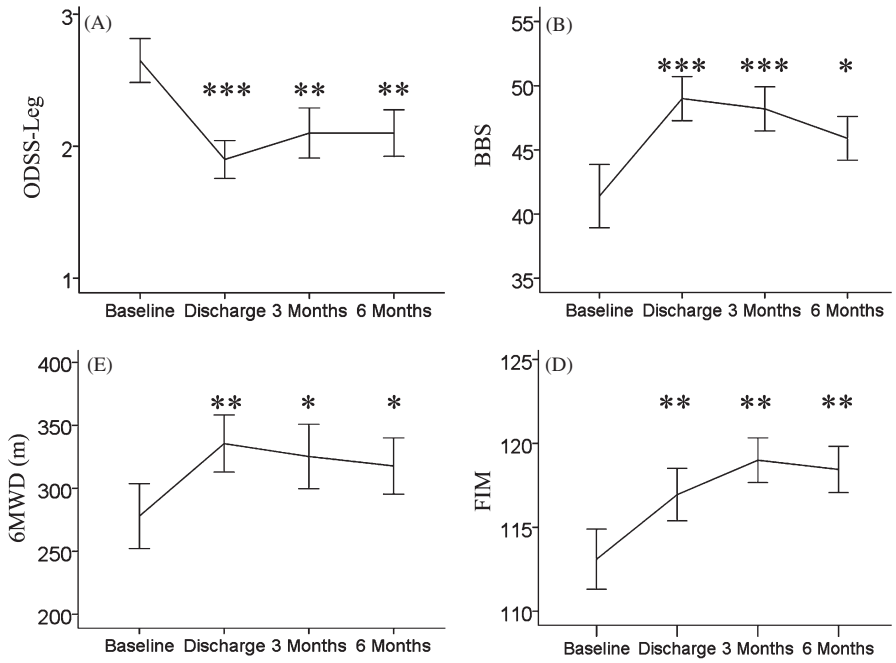

Figure 1. Functional measure changes over time after exercise in sensory ataxic neuropathic patients. There is a significant change over time, compared with baseline examination, of the functional measures ODSS-leg (A), BBS (B), 6MWD (C) and FIM (D). ODSS-leg, overall disability sum score, leg subscale; BBS, Berg balance scale; 6MWD, 6-min walk distance; FIM, functional independence measure scale. $^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0005$ vs. baseline examination. Values are mean ± 1 SEM.

program design, which did not include any systematic exercise maintenance programs after completion of hospital-based rehabilitation.

Disability and functional recovery was accompanied by an improvement of HRQoL, and specifically of the summary score PCS at 3-month follow-up and of the PF scale at the end of the rehabilitation period; the same scales were improved after a community based exercise intervention in patients with stable motor inflammatory neuropathy *(Graham et al., 2007)*. We also observed a significant improvement of the RF scale, consistent with a previous study *(Ruhland and Shields, 1997)*. The improvement was significant at 3-month follow-up, but not at 3-week, coherently with the assumption that the RF scale would measure self-perception of physical disability pertaining to problems with work or other regular daily activities *(Ware et al., 2000)*.

The concept of the minimum clinically important difference (MCID) represents the smallest improvement considered worthwhile by a patient and has been introduced as a way of overcoming the shortcomings of the "statistically significant difference" *(Copay et al., 2007)*. Although there is no literature consensus either on the definitions or in methodology for determining MCID, it has been found that the value of 0.5 SD corresponded to the MCID across a variety of studies *(Norman et al., 2003; Revicki et al., 2008)*. According to this definition, most of the above-reported 3-month improvements would be considered as clinically meaningful.

Among the strengths of this single centre pilot study is that, differently from previous reports, we selected a study population of neuropathic patients whose functional impairment was secondary to sensory ataxia, and not to muscle weakness. Moreover, follow-up was longer and impairment, functional, disability, and HRQoL measurements were included as outcome measures. However, the study design was influenced by recognised factors which make recruitment into a randomised research study difficult *(McDonald, 2002; White et al., 2004; Graham et al., 2007)*. The nature of exercise interventions is such that randomisation to intervention vs. control groups may not be acceptable to many participants and may interfere with aspects of the complex intervention prescribed *(Hawe et al., 2004; Graham et al., 2007)*. Moreover, sensory ataxic neuropathic patients, with stable disease and no disqualifying medical conditions, are relatively rare, further limiting the study's sample size. The nature of the study also made it not possible to blind patients and treating therapists; however, two independent evaluators, maintained blinded as much as possible, rated the different outcome measures and results were consistent. We therefore acknowledge that the design chosen introduces potential bias and

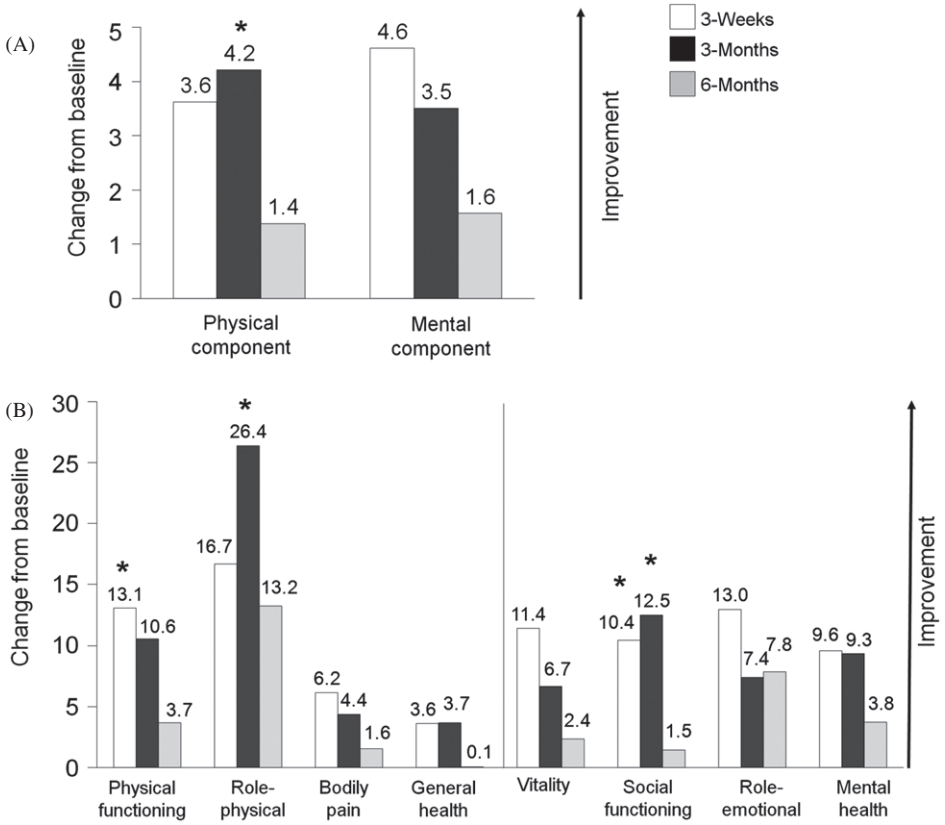

Figure 2. Quality of life improvement in the training group. After a 3-week intensive exercise program, a general improvement of mean Medical Outcome Study 36-item short-form health status scale (SF-36) summary scores (A) and scales (B) values is observed. There is a significant improvement in the summary measure physical component summary score (PCS) at 3-month follow-up (A); the improvement in the physical functioning (PF) scale is significant at the end of treatment, the improvement in the Role-physical scale (RP) is significant at 3-month follow-up, the improvement of the social functioning scale (SF) is significant at 3-week and 3-month follow-up. $^{*}p < 0.05$ vs. baseline examination.

that the interpretation of the results should be viewed with appropriate caution.

In conclusion, this pilot study suggests that a 3-week intensive balance and treadmill exercise is safe and well tolerated and might be effective in ameliorating disability, functioning and HRQoL in patients affected by chronic peripheral sensory ataxia, thus supporting the need for larger, randomised, controlled clinical trials in order to prove the efficacy of this therapeutic approach. Furthermore, the specific contribution of balance training in patients affected by sensory–motor neuropathy, in which disability is secondary to both muscle weakness and sensory ataxia, will also need to be assessed.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study flow chart. Patient recruitment was performed according to pre-established inclusion and exclusion criteria. *Two patients affected by chronic inflammatory demyelinating neuropathy relapsed and were treated with intravenous immunoglobulin therapy; one of them was lost at follow-up.

Table S1. Efficacy of exercise in sensory ataxic patients.