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Original article

Factors influencing balance improvement in multiple sclerosis rehabilitation: A pragmatic multicentric trial

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ABSTRACT

Objectives: Treatment for progressive multiple sclerosis (pMS) is a key area of research. To date, whether MS type and the rehabilitation setting are associated with worse or better response to rehabilitation is unclear. We aimed to understand the association between balance and MS type, in/outpatient treatment and specificity of the intervention.

Methods: We assessed 150 people with MS before and after in/outpatient rehabilitation. The Berg Balance Scale (BBS) was used to discriminate between responders ($\geq$ +3-point improvement in BBS score; a clinically meaningful improvement) and non-responders to specific or non-specific balance rehabilitation. Factors associated with balance were analyzed by univariate and multivariable logistic regression analyses, estimating odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Balance improved after rehabilitation: median (quartile 1 [Q1]–Q3) BBS score pre- and post-rehabilitation of 49 (45–53) and 52 (47–55) ($P < 0.001$). Univariate logistic analysis revealed a clinically meaningful improvement in balance associated with pMS (OR 2.21 [95% CI 1.09–4.05]), inpatient therapy (0.41 [0.19–0.84]), using a walking aid (1.68 [1.06–2.69]), and low baseline BBS score (0.86 [0.81–0.92]). On multivariable analysis, probability of improvement was similar for participants with pMS and the relapsing-remitting form but was associated with low baseline BBS score and specific treatment (OR 0.81 [95% CI 0.74–0.89] and 5.66 [1.79–21.5]).

Conclusion: A clinically meaningful improvement in balance was more likely when MS individuals with moderate to high disability had specific exercises targeting balance, but MS type did not influence the outcome.

1. Introduction

Studies of people with multiple sclerosis (PwMS) with a progressive form are scarce, [1] and more information is needed when selecting potential treatment options intended to improve mobility and quality of life. Commentaries and reviews have supported the effectiveness of rehabilitation in reducing disability and improving mobility [2,3] in PwMS; however, results from randomized controlled trials are often contradictory, in particular for people with progressive MS (pMS) [4–7]. The identification of factors associated with positive improvements from rehabilitation interventions, such as MS type, specificity of the intervention, or setting (in/outpatient rehabilitation) would inform the development of effective rehabilitation interventions. Furthermore, it would enhance our understanding of how rehabilitation works and how to better allocate resources with targeted interventions.

In the past decades, a few studies have investigated predictors of outcomes from rehabilitation, with contradictory results. Long disease duration is commonly considered a predictor of reduced benefit of rehabilitation, along with more severe pyramidal, cognitive, sensitive, verbal and cerebellar impairments, which are often characteristic of pMS [8]. A few studies reported better outcome in PwMS with a relapsing-remitting course, short disease duration and mild to moderate disability [1,9]. However, Liberatore et al. [10] indicated increased probability of improvement for PwMS with moderate to severe involvement of motor

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factors and higher Expanded Disability Status Scale scores after a multidisciplinary rehabilitation. Further clarification of the influence of disease duration, disability level and MS type on rehabilitation is needed.

To our knowledge, only one study systematically reviewed the evidence for the effect of in/outpatient settings on rehabilitation outcome and quality of life [11].

A drawback of published studies is the lack of accepted outcome measures sensitive to change and with defined clinically important improvements. The widely used Expanded Disability Status Scale has poor sensitivity to change and thus may not be able to detect improvements after a short period of rehabilitation [12]. The Berg Balance Scale (BBS) is considered one of the key scales to measure balance disorders in MS. The scale has been used in many studies to describe balance status and measure changes in response to various interventions. A +3-point improvement in score denotes an established minimal clinically important difference (MCID) defining a clinically meaningful improvement after rehabilitation for PwMS [13]. By using this MCID as a cut-off, we can develop predictive models to identify people with a probability of meaningful improvement after rehabilitation and to test whether MS type, level of mobility limitations and in/outpatient rehabilitation can predict improvement, taking into account other confounding variables such as age, sex and disease duration.

Rehabilitation interventions frequently include clinical strategies to improve balance in PwMS because balance deficits are associated with negative consequences such as falls and fear of falling [14,15], gait disturbance [16], and activity curtailment [17,18]. Rehabilitation of balance is particularly important for PwMS with pMS because pharmacological treatments effective for delaying disability progression are scarce. A recent review reported the efficacy of home or outpatient balance rehabilitation for improving balance in PwMS [11]. However. a more extensive analysis of the literature revealed controversial results, with some clinical studies of outpatients showing improvement in balance leading to reduced number of falls[19,20], which was not confirmed in other studies including similar populations [5].

Thus, the aim of this study was to assess whether MS type, a specific intervention and setting (in/outpatient rehabilitation) can predict balance improvement after rehabilitation.

2. Methods

2.1. Participants and setting

In the present retrospective study, we merged data from preceding randomized clinical trials or longitudinal studies [5,21,22] conducted from February 27, 2006, to September 7, 2013, and ongoing clinical trials of PwMS. Participants were admitted in 2 clinical centres for physical therapy and rehabilitation located in Italy and Ireland. Inpatient and outpatient participants were recruited from the centres' in-hospital and ambulatory services. Eligible participants were PwMS who required rehabilitation to maintain balance or to improve it after balance worsening, who received rehabilitation treatment and who fulfilled the following inclusion criteria: diagnosis of MS according to Poser and McDonald criteria [23]; age 18 to 75 years; no medical conditions precluding rehabilitation participation (based on clinical judgment), able to stand independently for 30 sec and walk (with/without aid) for 6 m, and having a baseline and post-rehabilitation assessment including all predictors used in this study. Exclusion criteria were the ability to stand in monopodalic position for more than 10 sec and presence of cognitive disorders hampering the execution of the exercises/assessment (based on clinical judgment).

Baseline assessments were performed by an evaluator the day before starting the rehabilitation program, and the post-assessment was performed at the end of the rehabilitation program. There were no follow-up data. Only 2 of 3 evaluators were blinded to allocation of participants to a specific intervention. To determine clinical predictors of improvements, we divided the whole group into 2 sub-groups, responders and non-responders to rehabilitation, according to the 3-point BBS cut-off score (MCID) [13,24,25].

2.2. Predictors of improvement and rehabilitation procedure

We chose predictors on the basis of preceding studies (Table 1) [9–11]: age, sex and years since disease onset; MS type (pMS or non-progressive); use of a walking aid; rehabilitation setting (see description below); number of falls in the 3 months preceding the study (a fall was defined as "an episode of unintentionally coming to rest on the ground or lower surface that was not the result of

Table 1
Clinical and demographic characteristics of the whole sample and inpatients and outpatients with multiple sclerosis (MS).

	Whole sample ($n = 150$)	Outpatients $n = 106$ (71)	Inpatients $n = 44$ (29)
Age (years), mean (SD)	47.5 (11.2)	47.3 (11.7)	45.6 (9.8)
Sex, n (%)			
Men	47 (31)	34 (32.0)	13 (29)
Women	103 (69)	72 (68)	31 (70)
Disease duration (years), mean (SD)	11.8 (7.7)	12.2 (8.4)	12.2 (6.3)
MS type[a], n (%)			
Benign	3 (2)	3 (3)	0 (0)
Relapsing-remitting	80 (57)	63 (64)	17 (41)
Secondary progressive	43 (31)	20 (20)	23 (56)
Primary progressive	14 (10)	13 (13)	1 (2)
Specific/unspecific treatment, n (%)			
Specific	117 (78)	86 (81)	30 (68)
Unspecific	33 (22)	20 (19)	13 (29)
Walking aid, n (%)			
None	99 (66)	66 (62)	28 (64)
Unilateral	37 (25)	30 (28)	6 (14)
Bilateral	14 (9)	10 (9)	10 (23)
History of falls, median (Q1–Q3)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Berg Balance Scale score, median (Q1–Q3)			
Baseline	49.0 (45.0–53.0)	51.0 (47.0–55.0)	46.0 (40.5–49.5)
Post-rehabilitation	52.0 (47.0–55.0)	53.0 (49.0–56.0)	49.0 (44.0–53.0)

[a] missing data, $n = 10$.

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dizziness, fainting, sustaining a violent blow, loss of consciousness or other overwhelming external factor" [26]); baseline BBS score; and specificity of the intervention (participants receiving specific treatment for balance disorders were considered as having specific balance training; details of the intervention can be found elsewhere [19–21]. The remaining sample received non-specific treatment that also included balance training).

For rehabilitation setting, in the Italian sample, outpatients received 20 physical therapy treatments lasting 45 min for 2 or 3 times/week and inpatients received the same amount of treatment 5 times/week. In the Irish sample, routine physiotherapy was provided to outpatients once per week with an added exercise program including individual sessions or group classes (or a combination of these interventions) for 8 weeks as detailed elsewhere [22]. The sessions were supervised by a physical therapist. The participants did not receive any rehabilitation before the respective programs. Inpatients were involved in other therapies (e.g., speech or neuropsychological therapy), but data on these treatments were not collected.

2.3. Statistical analysis

Data are reported as numbers (%), mean (SD) or median (quartile 1 [Q1]–Q3). To assess the association between predictors and response (a clinically relevant improvement in balance), we used univariate logistic regression models with responder/non-responder as a dichotomous dependent variable and MS type, setting and specificity as predictors along with variables listed in Table 1. To assess the multiple contributions of collected variables in predicting response, we used multivariable logistic regression models including the main variables of the study: MS type, setting and specificity. Odds ratios and 95% confidence intervals (CIs) were estimated. We also included variables in the model showing a significant association between predictors and response at $P < 0.05$ on univariate analysis.

We checked for presence of influential points and distribution of residuals. One individual with a large leverage was removed from the analysis. Information explained by the model was calculated by the McFadden's measure for multinomial and ordered logit, providing pseudo-R^2 values. We also checked for collinearity among predictors by using pair-wise correlation plots among different predictors and calculating the variance inflation factor by using the pseudo-R^2 values. A variance inflation factor < 4 is considered good for a model.

The Wilcoxon test was used to compare BBS scores for the overall sample pre- and post-rehabilitation. $P < 0.05$ was considered statistically significant. Finally, receiver operating characteristic (ROC) curve analysis was used for BBS prediction, and the area under the ROC curve (AUC) is reported. R (2008) (R Foundation for Statistical Computing, Vienna, Austria) was used for analysis.

3. Results

The study included 150 PwMS; 103 (69%) were women (Table 1). The mean (SD) age was 47.5 (11.2) years and mean disease duration 11.8 (7.7) years. In total, 51 (34%) participants required an assistive device to walk and 48 (32%) reported at least one fall; 21 (14%) were repeat fallers (> 1 fall).

The median (Q1–Q3) BBS scores pre- and post-rehabilitation for the whole sample were 49 (45–53) and 52 (47–55) (Wilcoxon test, V = 1027, $P < 0.001$). Overall, 90 (60%) participants had at least a 1-point improvement in BBS score after treatment, 75 (50%) had a 2-point improvement and 55 (37%) had a clinically relevant improvement of ≥ 3 points.

On univariate analysis, the probability of a clinically relevant improvement was associated with inpatient therapy (setting), having pMS, and using a walking aid (Table 2).

A clinically relevant improvement was associated with low baseline BBS score (Table 1), with an AUC of 0.79 (95% CI 0.72–0.86). To test whether this finding could be due to a BBS ceiling effect, we removed PwMS participants with baseline BBS scores > 49 (*n* = 78, median BBS score 45 [range 14–49]), but the results were similar (baseline BBS score: OR 0.93 [95% CI 0.87–1.00], $P = 0.08$).

The multivariable model included MS type, setting, specificity of the intervention, use of a walking aid and baseline BBS score (Table 3). Probability of a clinically significant improvement in balance was associated with receiving specific treatment (OR 5.66 [95% CI 1.79–21.51], $P < 0.01$) but not pMS type (0.69 [0.30–1.58], $P = 0.37$) or use of a walking aid (0.48 [2.21–0.99], $P = 0.06$) and was associated with low baseline BBS score (0.81 [0.74–0.89], $P < 0.001$).

To better represent differences between responder groups, Table 4 reports the proportion of responders to specific and unspecific balance rehabilitation for participants with high or low BBS baseline scores.

Finally, the Fig. 1 shows the probability of a clinically significant improvement in balance by baseline BBS score for MS type and specific/non-specific balance intervention. In Fig. 1B, the probability of a ≥ 3-point improvement in BBS score for an hypothetical individual with a baseline BBS score of 40 with specific treatment for mobility disorders was about 87% (SE 0.06). This probability decreased to 33% (0.09) with a baseline BBS score of 40 with a non-specific intervention. Likewise, for 2 hypothetical individuals receiving specific treatment for mobility and balance disorders, with baseline BBS scores of 40 and 50, the probability of a ≥ 3-point improvement in BBS score was 86% (0.06) and 31% (0.05), respectively.

4. Discussion

The aim of this study was to assess whether MS type, specificity of intervention and setting could predict improvement in balance

Table 2
Univariate logistic analysis of factors associated with a clinically meaningful improvement in balance.

	N	Estimate	Standard error	OR (95% CI)	*P*-value
Main predictors					
MS type (ref. progressive MS)	140	0.79	0.35	2.21 (1.09–4.05)	0.03
Specific/unspecific (ref. specific)	150	−0.40	0.42	1.49 (0.66–3.54)	0.35
Setting (in/outpatient) (ref. outpatient)	150	−0.88	0.37	0.41 (0.19–0.84)	0.02
Other covariates					
Age (years)	150	0.01	0.02	1.01 (0.98–1.04)	0.45
Onset (years)	150	0.01	0.01	1.01 (0.99–1.03)	0.57
Sex (ref. male)	150	−0.34	0.37	0.71 (0.34–1.45)	0.36
Baseline BBS score	150	−0.14*	0.03	0.86 (0.81–0.92)	< 0.001
Walking aid	150	0.52	0.23	1.68 (1.06–2.69)	0.03
Baseline falls	150	−0.03	0.09	1.02 (0.85–1.22)	0.76

Q3 OR: odds ratio, 95% CI, 95% CI; BBS: Berg Balance Scale; Ref: responder.

Table 3
Multivariable logistic analysis of factors associated with a clinically meaningful improvement in balance ($n = 140$).

	Estimate	Standard error	OR (95% CI)	*P*-value
MS type (ref. progressive)	−0.37	0.42	0.69 (0.30–1.58)	0.37
Specific/unspecific (ref. specific)	1.73	0.62	5.66 (1.79–21.51)	< 0.01
Setting (ref. outpatient)	−0.08	0.48	0.92 (0.36–2.41)	0.86
Baseline BBS score	−0.2	0.05	0.81 (0.74–0.89)	< 0.01
Walking aid	−0.72	0.38	0.48 (2.21–0.99)	0.06

OR, odds ratio; 95% CI, 95% confidence interval; BBS: Berg Balance Scale. Ref, responder; Log-likelihood: −72.45814 (df = 6), pseudo-R^2: 0.21. Variance inflation factor = 1.26.

Table 4
Percentages and [mean BBS change] of individuals with a clinically significant improvement according to initial BBS score and specificity of treatment.

	BBS score pre-intervention	
	0–45	46–56
Non-specific	50% (2.0)	15% (−0.1)
Specific	78% (7.3)	26% (1.4)

BBS: Berg Balance Scale.

after rehabilitation for PwMS. Overall, the data show improvements in balance after rehabilitation for these individuals, and probability of improvement was similar for people with pMS and relapsing-remitting MS whether treated as an in/outpatient.

Multivariable analysis revealed that the specificity of intervention was the most important predictor of a clinically meaningful improvement, highlighting the importance of specific and tailored treatment as compared with generic exercises. Furthermore, individuals with more impaired condition benefited more from the rehabilitation treatment. The association between the specificity of the intervention and impairment at baseline and rehabilitation outcome was evident considering the proportion of treatment responders. Within this group, almost 80% of participants with low balance performance at baseline showed improvement if the rehabilitation was specifically aimed at improving these aspects, whereas participants with better baseline performance showed less response, with only 26% of those receiving specific rehabilitation showing clinically meaningful improved balance.

When controlling for level of balance impairment, we found no effect of type of MS, which highlights that people with pMS can attain the same functional improvements as those with relapsing-remitting MS. This finding is important because pMS is often associated with the development of severe and irreversible disability [27] and modifying drugs are not effective in preventing functional loss [28], so rehabilitation is the only viable solution to improve function.

Our results support findings from a systematic review of treatments for pMS revealing that physiotherapy has a small but significant beneficial effect on balance [29]. The authors pointed out that the evidence for the effects in severely disabled persons are still missing. However, our findings reveal a negative association between improvement and balance impairments as measured by the BBS when specific exercises are used, which suggests a beneficial effect of that approach. Future randomized controlled trials should investigate this hypothesis and the maintenance of the observed effect after the end of treatments.

Differences in demographic and baseline characteristics need to be considered when comparing our data with results from other studies. Carling et al. found a 4-point improvement in BBS score after 14 treatment sessions in older PwMS with progressive disease, with an average BBS baseline score of 31 and 86% of people using walking aids [30], and Gandolfi et al. found a 5-point improvement in BBS score in a sample with similar age, disease duration and BBS baseline score [19]. More in line with our results, Sosnoff et al. found a 3-point improvement in BBS score in an older sample with similar disease duration and proportion of people using a walking aid [31].

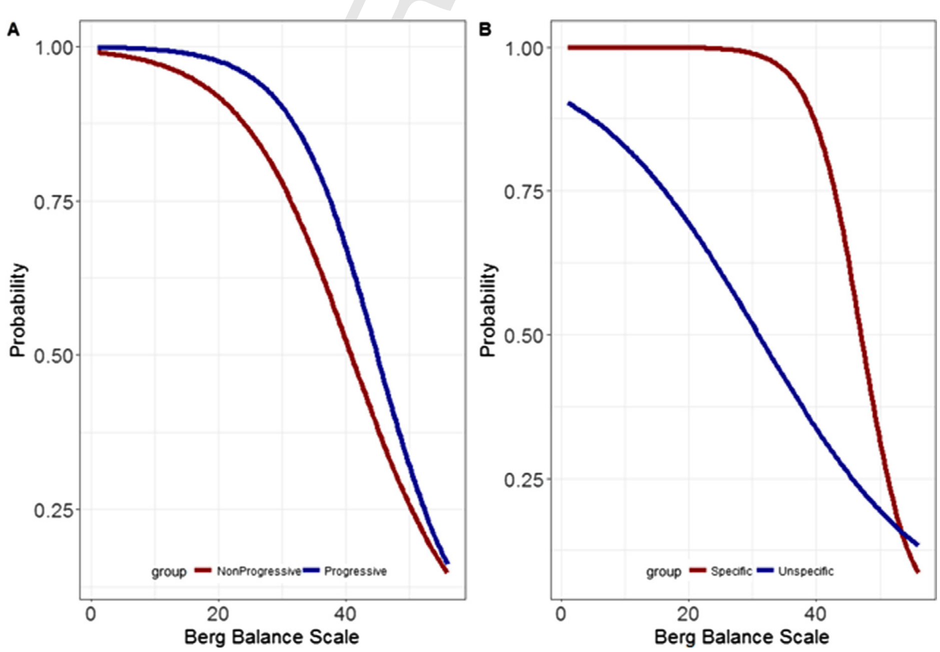

Fig. 1. Probability of a clinically significant improvement in balance by baseline Berg Balance Scale score and multiple sclerosis type (A) and specific/non-specific balance interventions (B).

Rehabilitation setting was found associated with improvement only on univariate analysis, with inpatients showing improvement more than outpatients. This finding agrees with other studies showing positive effects of rehabilitation on balance disorders for inpatients [9,20,21]. This result may be due to inpatient functional rehabilitation often being coordinated by specialized interdisciplinary teams and inpatients having higher treatment intensity. Despite these advantages of inpatient rehabilitation, setting did not remain a predictor of improvement in the multivariable model. The results from univariate analyses were probably biased by different levels of mobility balance disorders and other factors such as the quantity and content of care provided. Differences between settings should be further investigated with a larger outpatient sample and a multivariable assessment to fully appreciate its effects because inpatient rehabilitation generally addresses multiple functional needs.

In our study, the degree of balance disorder at baseline predicted a clinically relevant improvement in balance performance after rehabilitation [13]. This result supports findings from a study finding that individuals with more mobility disorders and activity limitations showed greater beneficial effect from rehabilitation [9]. Altogether, the results suggest that even individuals with moderate to high levels of disability can show improved balance after rehabilitation and that PwMS should receive treatment regardless of age, sex and time since diagnosis. This finding expands the range of people who can receive treatment but also suggests that other forms of treatment should be developed for highly functional PwMS.

One concern was that the observed association between BBS score and clinically relevant improvement might be due to the well-known ceiling effect of the BBS [22]. This concern was partially ruled out because the association between baseline BBS score and improvement remained on analysis of a sub-sample of individuals not presenting ceiling effects.

Finally, a walking aid was associated with increased probability of improvement on univariate analysis. However, this trend was not confirmed in the multivariable model. Further studies are needed to understand whether this association is due more to impaired individuals being more likely to use a walking aid or if this variable can be an independent predictor of improvement.

A strength of this study is the large sample size obtained by combining data from 2 countries and that the data considered both inpatient and outpatient rehabilitation. The framework of a pragmatic clinical trial such as the present study produces results that can be generalized to routine practice settings but is also open to a variety of biases. First, BBS does not assess all the expected benefits of rehabilitation, and future studies including a multidimensional assessment are needed. Second, because only 2 of 3 evaluators used in the 3 studies were blinded to participant allocation and we did not use a control group not receiving rehabilitation, this retrospective analysis cannot provide information on the efficacy of rehabilitation. A further limitation is the difference between settings (intensity of treatments, presence/absence of caregivers) that can influence improvement of function and that could not be accounted for. Finally, caution should be made to generalize our findings to individuals with different features because we recruited only participants able to stand for 30 sec and walk at least 6 m; no information is available for early-diagnosed individuals or those with severe impairment.

5. Conclusion

Our data suggest a significant improvement in balance after rehabilitation interventions for PwMS. We observed an association between specificity of treatment and good rehabilitation outcome. Increased level of disability but not MS type was associated with improved balance, which indicates the utility of rehabilitation for both relapsing-remitting and pMS.

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Disclosure of interest

The authors declare that they have no competing interest.

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