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Short communication

Physiotherapy improves motor function in patients with the Parkinson variant of multiple system atrophy: A prospective trial

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ABSTRACT

Background and objectives: Gait impairment and reduced mobility are disabling symptoms of multiple system atrophy. While physiotherapy is increasingly recognized as a valuable supplement to pharmacotherapy for patients with Parkinson's disease, data on the efficacy of physiotherapy for multiple system atrophy are lacking. This study aimed to explore the feasibility of two consecutive exercise-based interventions in patients with multiple system atrophy.

Subjects and Methods: We included 10 patients with the parkinsonian variant of multiple system atrophy and 10 patients with Parkinson's disease, matched for gender and Hoehn & Yahr stage (≤ 3). Interventions consisted of a five-day inpatient physiotherapy program followed by a five-week unsupervised home-based exercise program. Outcomes included instrumented gait analysis, patient questionnaires, clinical rating scales and physical tests. Patients were examined at baseline, after the first inpatient treatment and again after the home-based intervention. Additionally, a structured telephone interview was performed immediately after the second intervention period.

Results: Both patient groups exhibited a similar improvement of gait after the interventions, as measured by instrumented gait analysis. These effects reached their maximum level after inpatient physiotherapy and remained stable following the home-based exercise program. Patient questionnaires also showed improvements after the interventions, but motor clinical rating scales did not.

Conclusion: Our pilot results suggest that a short-term bout of physiotherapy is feasible, safe and improves gait performance in patients with multiple system atrophy. This highlights the potential of physiotherapy for this disabling condition where pharmacotherapy typically achieves poor effects. The present findings warrant a larger controlled study.

1. Introduction

Gait impairment and reduced mobility represent pivotal symptoms of both Parkinson's disease (PD) and the Parkinson variant of multiple system atrophy (MSA-P), the latter typically developing earlier, being more severe and markedly less responsive to dopaminergic therapy [1]. In PD multiple controlled trials have established the efficacy of exercise-based interventions and the European Physiotherapy Guideline for PD provides evidence-based information for physiotherapists and physicians [2]. In contrast, only little information exists about physiotherapy in MSA patients [3]. Thus, it remains unknown whether physiotherapy for MSA patients is useful and, if so, what exercise strategy should be recommended. Therefore, the present study aims to explore the safety, feasibility and preliminary effects of physiotherapy for patients with MSA using instrumented gait analysis, clinical rating scales, patient-rated questionnaires and physical tests as outcomes. As a

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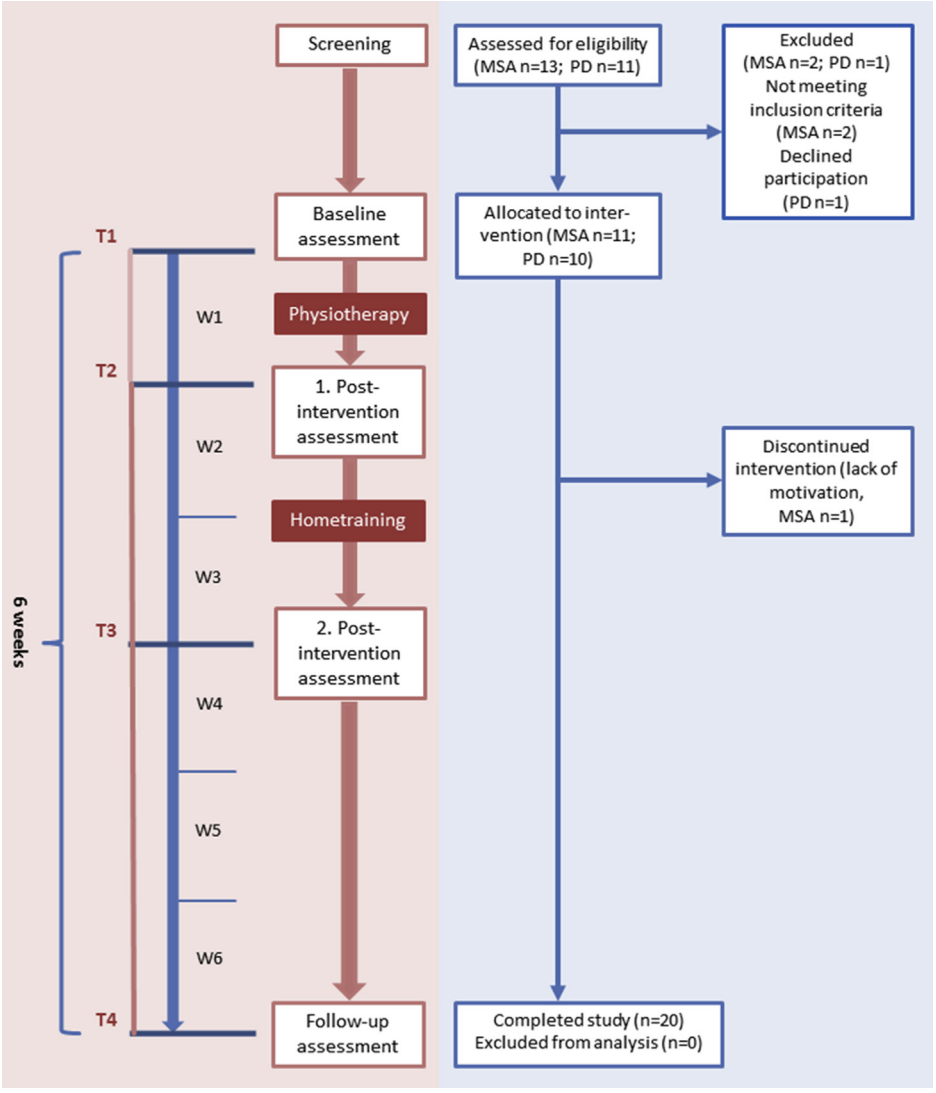

Fig. 1. Study design and flow-chart.
T: Timepoint; W: Week. Patients' assessment was performed at three different time points in the hospital and was structured as follows: baseline (T1) at day 0, the first post-intervention assessment (T2) immediately after the 5-day inpatient physiotherapy (day 5) and the second one (T3) after the first two weeks of the unsupervised home-based exercise (day 19). T1, T2 and T3 consisted of instrumented gait analysis in lab, clinical rating scales, and patients' questionnaires. A structured follow-up with phone-call interview concluded the overall intervention period after 6 weeks (T4, day 40) and was performed by the study investigator.

first step, we investigated the effects of intensive inpatient physiotherapy in MSA and matched PD patients. Secondly, we evaluated whether any short-term effects were sustained after a home-based exercise intervention. PD patients served as controls since the effectiveness of the adopted intervention is well established for this patient group, and – assuming that MSA is less amenable to treatment– we expected to see between-group differences in favor of PD over the intervention period.

2. Methods

A pilot two-arm pre-post study was conducted at the Movement Disorder Unit, Medical University Hospital Innsbruck, Austria. It was approved by the local ethics committee (IRB-approval–No 0365, 344/4.25 378/5.3, 20.10.2017). Participants gave written informed consent prior to participation.

2.1. Participants and design

The study flow chart and design are illustrated. Between June 2017 and June 2018, 20 non-demented patients were enrolled at the Movement Disorder Unit, Medical University Hospital of Innsbruck, Austria. Patients were matched for gender and Hoehn and Yahr (H&Y) stage and diagnosed according to the criteria for MSA [4](probable MSA-P n = 10) and PD (n = 12) [5]. Additional inclusion criteria were age (30–80 years), stable doses of dopaminergic replacement therapy and orthostatic hypotension (OH) pharmacological/non-pharmacological treatment for at least three weeks prior to recruitment, ability to walk unassisted, no hearing or visual problems interfering with walking or testing. Exclusion criteria consisted of non-parkinsonian gait impairment, severe dementia, H&Y stage 4–5, recent surgery, deep brain stimulation, unstable coronary artery disease, history of freezing of gait and severe motor fluctuations. All patients were investigated between 10:00 and 13:00 in stable ON medication without presence of motor fluctuations. Every visit was performed by an expert neurologist, physical tests following each study visit were delivered by a physiotherapist completely blinded to the pre/post intervention status. Motor parts of MDS-UPDRS (for all patients) and of UMSARS (for MSA patients) were video-rated by a neurologist who was blinded to pre/post intervention status.

2.2. Intervention

Supervised strength, flexibility, posture and balance exercises, transfers, swings, walking and coordination training, dual task and stair climbing were performed for 60 min for 5 days, followed by home-based 60-min exercise for 5 days per week for 2 weeks. Including a 3-week follow-up period the overall study duration was 6 weeks. Intervention details (S1) and protocol (S2) are shown as supplementary material. Adherence was determined using patients' diaries and cross-

checked with the patients/caregivers during weekly phone calls, which were also used to monitor and record any adverse events.

2.3. Clinical rating scales

Disease severity was measured by H&Y staging [6] and MDS-UPDRS [7]. UMSARS [8] was administered in MSA patients. Cognition was assessed using the Montreal Cognitive Assessment (MOCA) [9]. The Parkinson's Disease Questionnaire (PDQ-39) [10] was employed to evaluate quality of life and the Orthostatic Hypotension Questionnaire (OHQ) [11] to measure orthostatic symptoms. The Patients' Global Impression of Change (PGIC) [12] scale was conducted to quantify patients' perception of gait change. The telephone interview included MDS-UPDRS parts 1 and 2, UMSARS part 1, the PDQ-39 and PGIC.

2.4. Physical tests and instrumented gait analysis

Balance was assessed using the Berg Balance Scale (BBS) [13]. Dynamic balance and mobility were explored by the Timed Up and Go Test (TUG) [14]. Gait velocity was assessed using the 10-Meter Walk Test (10MWT) at maximum speed [15]. Instrumented gait analysis was performed using wearable sensors (Shimmer Research Ltd., Dublin, Ireland) attached to the posterolateral part of both shoes. Spatiotemporal gait parameters such as gait velocity, stride length, maximal toe clearance, stance and swing times were obtained using pattern recognition algorithms [16].

Feasibility of the sensor-based gait analysis system of detecting motor impairment in patients with PD and APD has previously been demonstrated and validated from a technical and clinical perspective. Particularly, gait velocity and stride length were previously demonstrated to support clinical differential diagnosis between APD and PD patients [17] therefore, we used the sensor-based gait analysis system as primary outcome. Patients were instructed to walk 10 m at a self-selected ("normal gait"), fast and slow speed, the latter two representing "challenged gait", being defined as the fastest/slowest but comfortable velocity for the patient. No walking aids were used for testing.

2.5. Statistical analyses

Normal distribution of variables was checked using the Shapiro-Wilk test. Differences in categorical data were calculated using the Chi-square or Fisher's exact test. For continuous or demographic variables, the Mann-Whitney *U* test or *t*-test were used. Spatiotemporal gait parameters were analysed for within- and between-group differences using separate two-level linear mixed models. As fixed factors "group" (PD vs. MSA) and "time" (T1-T3) were used. Two-sided p-values were set at an alpha level of 0.05. PD and MSA data were analysed separately and for spatiotemporal gait parameters without significant between-group differences the data were pooled. For clinical rating scales, physical tests and questionnaires, the Friedmann test was adopted. Sustainability of training effects was evaluated by analysing gait changes from T1 and T2 to T3, respectively. Bonferroni post-hoc test was used to correct for multiple comparisons. Statistical analyses were performed using the IBM SPSS 25.

3. Results

Patient baseline characteristics are shown in Table 1. Patient groups were similar with respect to gender, H&Y stage, cognition (MoCA). Patients with PD were significantly older, showed longer disease duration and higher Levodopa Equivalent Dose (LEDD) [18] compared to MSA, who had higher MDS-UPDRS scores. Neither falls nor adverse events (e.g. muscle soreness, pain) were reported during the overall intervention period.

Table 1
Demographic and clinical characteristics of patients.

Patient characteristics	PD n = 10	MSA n = 10	P value
Age at examination, mean (SD)	71.6 (7.1)	57.4 (5.9)	< 0.05
Gender (m:f)	5:5	4:6	n.s.
Disease duration, mean (SD)	11.2 (8.4)	4.5 (2.2)	< 0.05
LEDD (mg/dl), median (IQR)	805 (350–1385)	237 (0–875)	< 0.05
Clinical rating scales			
Hoehn Yahr, median (IQR)	2.7 (2–3)	3 (2.7–3)	n.s.
MDS-UPDRS I, median (IQR)	7.5 (4–10.2)	13 (9.7–17)	< 0.05
MDS-UPDRS II, median (IQR)	4.5 (2–10.5)	18.5 (12.7–26.7)	< 0.05
MDS-UPDRS III, median (IQR)	23.5 (15.7–28)	27.5 (19.2–44)	< 0.05
UMSARS I, median (IQR)	–	18.5 (15–23)	–
UMSARS II, median (IQR)	–	17.5 (13.2–26.5)	–
MOCA, median (IQR)	26.5 (22–27)	28.5 (25.7–30)	< 0.05
Quality of life			
PDQ-39	3 (2.0–4.6)	7.1 (3.7–9.1)	< 0.05
Physical tests			
BBS, median (IQR)	53 (51.7–56)	50 (45.2–52.2)	< 0.05
TUG (s), median (IQR)	9.8 (6.8–11.3)	12.2 (8.3–14.5)	< 0.05
10 m WT, median (IQR)	7.6 (6.0–8.6)	9.2 (5.5–12.0)	< 0.05

SD Standard Deviation; IQR interquartile range; n.s. not significant; PD Parkinson's Disease; MSA Multiple System Atrophy; LEDD Levodopa equivalent daily dose; MDS-UPDRS MDS Unified Parkinson's Disease Rating Scale; UMSARS Unified Multiple System Atrophy Rating Scale; PDQ39 Parkinson's Disease Quality of Life 39; MOCA Montreal Cognitive Assessment; BBS Berg Balance Scale; TUG Timed Up and Go, 10 m WT 10 m Walking Test.

3.1. Instrumented gait analysis

Fig. S3 presents the relevant spatiotemporal gait parameters for normal (Fig. S3A) and challenged gait (Figs. S3B and C).

3.2. Normal gait

Fig. S3A presents spatiotemporal gait parameters at baseline (T1) and post-intervention (T2 and T3). Gait velocity improved after interventions in both MSA ($P = 0.03$) and PD patients ($P = 0.03$), without between-group differences ($P = 0.57$). Similar results were demonstrated for stride length (MSA, $P = 0.01$; PD, $P = 0.05$), without between-group differences ($P = 0.373$). The pooled analysis was significant ($F(2,15) = 11.93$, $P = 0.01$ for gait velocity and $F(2,15) = 13.83$, $P < 0.001$ for stride length). Maximal toe clearance improved in PD patients ($P = 0.008$) and only numerically in MSA patients ($P = 0.215$). Between-group differences were non-significant ($P = 0.121$), but results for pooled groups were statistically significant ($F(2,15) = 11.96$, $P = 0.001$). All three gait parameters improved between T1 and T2 (pooled $P < 0.001$), however, deteriorated between T2 and T3, statistically significant only for stride length (pooled $P = 0.017$). Post-intervention, the stance time percentage decreased in both groups ($P > 0.05$). The swing time percentage increased, without between-groups differences ($P = 0.71$). After pooling, statistical significance was reached (stance time percentage $F(2,15) = 4.53$, pooled $P = 0.029$; swing time percentage $F(2,15) = 4.53$, pooled $P = 0.029$). Similar to the spatiotemporal gait parameters, a difference was observed between T1 and T2 (pooled $P = 0.007$) but not between T2 to T3.

3.3. Challenged gait

Figs. S3B and C illustrate gait velocity, stride length and maximal toe clearance at baseline and post-intervention for fast and slow gait, respectively. An improvement in gait speed was observed post-intervention ($F(2,15) = 14.41$, pooled $P < 0.001$; $F(2,15) = 4.70$, pooled $P = 0.026$ respectively), without any between-group differences ($P = 0.99$; $P = 0.74$ respectively). Single-group analyses revealed an improvement in gait velocity (PD, $P = 0.013$; MSA, $P = 0.025$), but not

stride length (PD, $P = 0.196$; MSA, $P = 0.176$). Gait parameters differed between T1 and T2 (pooled $P = 0.008$ for stride length, pooled $P < 0.001$ for gait velocity) but not between T2 and T3.

The stance time percentage decrease and swing time percentage increase post-intervention were only numerical for fast gait. Maximal toe clearance improved in both groups between T1 and T2 and deteriorated between T2 and T3 ($F(2,15) = 2.42$; pooled $P = 0.12$). Pooled analyses showed improvement between T1 and T2 ($P = 0.049$).

During slow gait, no change was observed in any group.

3.4. Physical tests

Post-intervention, the BBS and TUG remained unchanged. Significant differences were observed for the 10MWT post-intervention in both MSA ($P = 0.018$) and PD patients ($P = 0.007$). Improvements were only seen from T1 to T2 (PD, $P = 0.011$; MSA, $P = 0.021$).

3.5. Clinical rating scales

MDS-UPDRS-3 and UMSARS-2 did not significantly differ post-intervention compared to baseline. UMSARS-1 significantly changed between T1 and T2 ($P = 0.01$), but these improvements were not stable over the home-based intervention period.

PDQ-39, OHQ and MoCA remained unchanged post-intervention compared to baseline. At T2, the median PGIC score for MSA and PD patients was 5 ("moderately better, slight improvement"), remained the same at T3 in MSA patients, while PD patients described their improvement as "somewhat better without any real difference" (PGIC = 4). At T4, MSA and PD patients reported a mean PGIC score of 4 and 5, respectively.

4. Discussion

Awareness of the importance of physiotherapy as a recognized therapy option for parkinsonian disorders is growing fast. Diverse exercise strategies have been well explored for PD patients whereas the effects of physiotherapy in MSA patients remain thus far unknown. Therefore, we investigated the feasibility, safety and impact of intensive inpatient physiotherapy combined with unsupervised home-based exercise on mobility in MSA patients.

Our results show that physiotherapy in both settings is safe and feasible. The interventions improved gait in both MSA and PD patients, as reflected by spatiotemporal gait parameters and the 10MWT. Specifically, gait velocity and stride length increased – suggesting an overall walking improvement. PGIC scales showed enhanced physical functioning, especially post inpatient intervention. Importantly, patients reported no falls during the intervention, but the observation period was only short.

Since gait impairment emerges early in the disease course of MSA and is resistant to pharmacotherapy, the potential to influence walking and balance through regular specific exercise is relevant indeed. Surprisingly, PD and MSA patients responded similarly to the interventions, despite MSA patients' higher baseline MDS-UPDRS scores. This suggests that the European Physiotherapy Guidelines for PD also apply to MSA-P patients. Of note, we demonstrated that walking improvement was greatest after the intramural physiotherapy and these effects were sustained after the two-week home-based training. Nonetheless, between T2 to T3, spatiotemporal gait parameters tended to revert. This indicates that the home-based intervention was less effective or simply a tapering of placebo effects in this uncontrolled study.

As emphasized by others, an important factor is a lack of motivation, a common barrier for engagement in exercise among people with PD. This highlights the importance of a truly patient-centered approach with continuous feedback and the need to include problem-solving strategies, coaching and education to enhance patients' motivation.

Another reason for the inferiority of home-based exercise could have been the absence of adjustments to the program. Despite patients' instructions including detailed written exercise descriptions independent training may well have been less compelling than intramural physiotherapy.

This study is not without limitations. Firstly, the sample size was small as the recruitment of MSA patients meeting the inclusion criteria was challenging for a monocentric study.

Secondly, due to Hoehn and Yahr matching, PD patients were significantly older and showed a longer disease duration, representing an important limitation for group comparisons. Owing to the different natural history and patients' characteristics of PD and MSA, for small studies a perfect matching is actually difficult to achieve. Another limitation of this work is the absence of blinding of the main investigator and patients, probably causing some bias, even if we employed blinded-video-rating, blinded physiotherapists for the physical tests and automated sensor-derived gait parameters as objective outcomes.

A future multicenter study is required to validate our findings, compare different physiotherapy approaches (duration, type, inpatient vs. home-based, frequency) regarding their benefits for MSA patients. Facilitating patients' independence and delaying the onset of gait impairment and reduced mobility represents a vital area for patients with MSA.

Ethical standards

This study has been approved by the local ethics committees in Innsbruck, Austria, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Disclosure statement

This was an academic and not an industry supported study. This work was performed at the Department of Neurology, Innsbruck Medical University, Innsbruck, Austria.

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Cecilia Raccagni reports one travel grant from MSA coalition.

Georg Goebel: nothing to declare.

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Roberta Granata: nothing to declare.

Jean-Pierre Ndayisaba: nothing to declare.

Barbara Seebacher: nothing to declare.

Gudrun Schoenherr: nothing to declare.

Jakob Mitterhuber: nothing to declare.

Pascalle Hendriks: nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.09.026.

Authors roles

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Research project: A. Conception, B. Organization, C. Execution;
Manuscript: A. Writing of the first draft, B. Review and Critique, C. Statistical Analysis.
Georg Goebel
Manuscript: Statistical Analysis.
Heiko Gaßner
Manuscript: B. Review and Critique.
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Manuscript: B. Review and Critique.
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Research project: C. Execution; Manuscript: C. Review and Critique.
Gudrun Sylvester Schoenherr
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