Impaired local dynamic stability during treadmill walking predicts future falls in patients with multiple sclerosis: A prospective cohort study

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ABSTRACT

Background: Falling is a significant problem in patients with multiple sclerosis (MS) and the majority of falls occur during dynamic activities. Recently, there have been evidences focusing on falls and local stability of walking based on dynamic system theory in the elderly as well as patients with cerebral concussion. However, in patients with MS, this relationship has not been fully investigated. The aim of this study was to investigate local stability of walking as a risk factor for falling in patients with MS.

Methods: Seventy patients were assessed while walking at their preferred speed on a treadmill under single and dual task conditions. A cognitive task (backward counting) was used to assess the importance of dual tasking to fall risk. Trunk kinematics were collected using a cluster marker over the level of T 7 and a 7-camera motion capture system. To quantify local stability of walking, maximal finite-time Lyapunov exponent was calculated from a 12-dimensional state space reconstruction based on 3-dimensional trunk linear and angular velocity time series. Participants were classified as fallers (≥1) and non-fallers based on their prospective fall occurrence.

Findings: 30 (43%) participants recorded ≥1 falls and were classified as fallers. The results of multiple logistic regression analysis revealed that short-term local dynamic stability in the single task condition (P < 0.05, odds ratio = 2.214 (1.037–4.726)) was the significant fall predictor.

Interpretation: The results may indicate that the assessment of local stability of walking can identify patients who would benefit from gait retraining and fall prevention programs.

1. Introduction

Falling represents a serious risk for patients with multiple sclerosis (PwMS); > 50% of patients have a history of at least one fall over a 6-month period (Gunn et al., 2013a; Kasser et al., 2011). To date, several risk factors for falling such as worse disability level, progressive type of disease, use of walking aids, impaired cognition, reduced walking speed and poorer balance performance have been identified in PwMS (Cattaneo et al., 2002; Gunn et al., 2013b; Nilsagard et al., 2009). Among those potentially modifiable risk factors, impaired walking has a high prevalence i.e., approximately 85% of patients with MS report gait disturbances as their main complaint (Bethoux and Bennett, 2011; Sosnoff et al., 2011; Tajali et al., 2017). Given the high frequency of falls and the incidence of fall-related injuries in PwMS, an early detection of mobility-related risk factors for falling is critical to allow timely interventions and to prevent the occurrence of recurrent falls in these patients.

Recently, there has been an increasing recognition that investigation of local dynamic stability (LDS) based on nonlinear dynamics can provide a deeper insight regarding the locomotor control and fall risk (Bruijn et al., 2013; Lockhart and Liu, 2008; Peebles et al., 2017). While traditional linear measures such as the range, standard deviation, and coefficient of variation of the time series provide information on the magnitude of variability within the system, nonlinear measures provide information on the temporal structure of the time series and variations of gait patterns over time (Dingwell et al., 2001; Dingwell and Marin, 2006; Stergiou and Decker, 2011). LDS can be assessed during normal walking using maximal finite-time Lyapunov Exponents (LyE) which quantify the rate of divergence between neighboring trajectories in a reconstructed state-space of the system’s dynamic (Bruijn et al., 2009;
Bruitin et al., 2010; Bruijn et al., 2013) The results of previous studies have revealed that measures of kinematic variability are not well correlated with measures of LDS that directly quantify the sensitivity of gait to small perturbations such as floor irregularities (Dingwell et al., 2001; Dingwell and Cavanagh, 2001).

Regarding the clinical application of LDS measures, it has been shown that LDS of walking is a more responsive index to show the effects of a gait training program in PwMS than other gait performance tests such as 10-meter walk, 3-minute walk and step frequency (Hilfiker et al., 2013). However, its ability to predict falls has not been fully investigated in PwMS. A study on the neurological patients with the paresis of the lower extremity including MS, stroke, traumatic brain and spinal cord injury patients showed that LyE discriminated well between patients with a low walking ability and healthy controls (Reynard et al., 2014). Nevertheless, the majority of these studies relied on retrospective or cross-sectional designs and the predictive value of LDS to identify fall risk has not yet been confirmed in PwMS (Lockhart and Liu, 2008; Peebles et al., 2017; Reynard et al., 2014; Toebes et al., 2012).

This issue is of great importance since prospective models of fall assessment identify the rate of falling in a certain time period in future, thereby identifying possible cause and effect relationship (Coote et al., 2014). In contrast, retrospective or cross sectional studies only reveal some kind of relationship between a number of factors and fall history.

In addition to the gait problems commonly reported by PwMS (Bethoux and Bennett, 2011; Comber et al., 2016), cognitive impairments also are experienced by 65% of PwMS (Gianni et al., 2014; Gunn et al., 2013a). Although there are a number of studies which have investigated the effects of dual tasking on LDS of walking in various populations (Fino, 2016; Lamothe et al., 2011; van Schooten et al., 2016), no studies have yet investigated the association between dual task tests of LDS and fall risk in PwMS. In the elderly, the results of a previous study revealed that LDS of walking decreased under a cognitive dual task condition (Lamothe et al., 2011). Moreover, the results of a recent study in the cerebral concussed patients demonstrated a significant decrease in the LyE under a cognitive dual task condition (Fino, 2016). However, none of these studies investigated the predictive ability of LDS measures under dual task conditions. This issue is important since walking in the real world requires paying attention to various environmental features and at the same time recovering from perturbations to avoid falls. Therefore, the purpose of the current study was to prospectively assess the predictive ability of LDS of walking and its dual task costs (DTCs) to identify fall risk in PwMS. Based on the current available evidences (Learmonth et al., 2016; Mofateh et al., 2017; Tajali et al., 2017; Wajda and Sosnoff, 2015), it was hypothesized that LyE and their dual task costs (DTCs) can predict future falls in PwMS. Information obtained from this study will help clinicians to prescribe fall treatment and prevention programs based on the underlying gait deficits in the single or dual task conditions.

2. Methods

2.1. Participants

Seventy PwMS were recruited from the Khuzestan MS Patients’ Society. Inclusion criteria were as follow: (2) a definite diagnosis of MS (of any subtype) as diagnosed by a neurologist, (2) an expanded disability status scale (EDSS, physician version) of 0 to 5.5, (3) no MS relapses 30 days prior to testing, and (4) the ability to walk independently for at least 2-min on a treadmill. Individuals who stopped repeatedly were excluded since a correct LDS assessment requires a minimal number of 85 consecutive gait cycles (Bruijn et al., 2013; Riva et al., 2014). Each participant signed an informed consent form that had been approved by the Internal Review Board of the University. Age, gender and the self-administered EDSS score for disease severity and other patients’ characteristics are reported in Table 1.

### Table 1

Demographic and clinical characteristics of non-faller and faller groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-faller</th>
<th>Faller</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants (%)</td>
<td>40 (57%)</td>
<td>30 (43%)</td>
<td>NA</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>33.12 (8.05)</td>
<td>35.48 (9.71)</td>
<td>0.29</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>34/6</td>
<td>15/15</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.21 (5.34)</td>
<td>23.76 (2.98)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>3.78 (4.00)</td>
<td>5.48 (5.38)</td>
<td>0.13</td>
</tr>
<tr>
<td>EDSS</td>
<td>3.15 (0.96)</td>
<td>4.18 (0.56)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Gait speed</td>
<td>1.80 (0.31)</td>
<td>1.68 (0.27)</td>
<td>0.11</td>
</tr>
<tr>
<td>Type of MS</td>
<td>Relapsing-remitting</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Secondary progressive</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Primary progressive</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note. Values are mean (standard deviation) or as otherwise indicated. EDSS: self-administered expanded disability status scale. NA: not applicable.

2.2. Procedures

Participants were assessed under the 2 experimental conditions, each lasting for 2-min: (1) single-task walking, (2) dual-task walking. Kinematic data were collected using a 7-camera motion capture system (Qualisys Inc., Sweden) at a sampling rate of 100 samples/s. Spherical retro-reflective markers, 10 mm in diameter, were attached to the heels bilaterally to calculate heel strike events. Moreover, a cluster of 3 infrared retro-reflective markers was placed on the floor in front of the participants to be able to calculate the 3D position of the heel. The speed of the treadmill was again increased and decreased in 0.1 km/h intervals to reconfirm the preferred speed (Mofateh et al., 2017). The speed of the treadmill was again increased and decreased in 0.1 km/h intervals to reconfirm the preferred speed (Mofateh et al., 2017). Participants were given enough rest before the actual experiment.

2.3. Data analysis

Maximum LyE were calculated to quantify LDS in this study (Bruijn et al., 2010). Firstly, trunk position data were filtered by a 4th order zero-lag Butterworth low pass filter with the cut off frequency of 20 Hz. Then, trunk linear velocities were obtained by differentiating the average position of trunk cluster markers while angular velocities of the trunk were calculated using the Euler method (Siciliano and Khatib, 2016). All analyses were performed on the velocity time series to minimize the effects of non-stationary in the position data.

Then, using a spline interpolation, linear and angular velocity time series of each trial were time normalized to n x 100 (n = number of strides) so that each stride approximately consisted of 100 samples. This issue is important since LyE algorithm is sensitive to both the number of strides and the number of gait cycles (Bruijn et al., 2010). Heel strike events were determined when the sign of heel marker anteroposterior (AP) velocity changed. To reconstruct the state-space, the
maximum available number of strides across all subjects was selected so that
each state space consisted of exactly the same number of samples. The
dimension of the state-space was 12 including linear, angular vel-
cocities and their delayed copies. Since after the time normalization,
time series contained the same number of samples and the same base
frequencies, a fixed time delay of 25 samples was used so that it rep-
resents a 90-degree phase shift equivalent to a derivative. Then, short
($\lambda_s$) and long ($\lambda_l$) time LyE were calculated from the reconstructed
state-space using Rosenstein’s algorithm. After that, the nearest neigh-
bor was identified for each point and the distances between trajectory-
tories were determined as a function of time. The divergence curves
were calculated from the reconstructed state-space and the average of
the logarithm of the divergence curves was determined. From this
curve, $\lambda_s$ and $\lambda_l$ were identified as the linear slopes over the duration
of one step and one stride respectively (Reynard et al., 2014).

Furthermore, in order to estimate cognitive motor interference, we
calculated dual-task cost (DTC) for $\lambda_s$ and $\lambda_l$:

$$DTC = 100 \left( \frac{S - D}{S} \right)$$

where $S$ equals single-task performance and $D$ is equal to dual-task
performance for each parameter.

2.4. Follow-up assessment of falls

In contrast to retrospective approach of fall assessment which
questions on the number of falls experienced several months before
testing and may be subjected to recall bias, prospective approach
measures the rate of falling in a certain time period after the initial
assessment (Coote et al., 2014; Gianni et al., 2014; Nilsagard et al.,
2009). Therefore, we define a time period of 6 months and follow-up
the rate of falling in this period. For this purpose, subjects were asked to
record their falls on the fall calendars and return these calendars at the
end of each month. In addition, they were contacted during the first
week of the fall count to remind them to count their falls.

For the purpose of patients’ monitoring, research assistants tele-
phoned each patient every 6 weeks, on average, to follow up each indi-
vidual’s fall data. A fall was defined as an unexpected event that re-
sults in ending up on the ground, floor, or any lower surface (Coote
et al., 2014; Tajali et al., 2017). Based on the previous studies, patients
were classified as fallers if they had reported one or more falls during
the 6-month follow up period (Gianni et al., 2014; Tajali et al., 2017).

2.5. Statistical analysis

Firstly, univariate logistic regression analysis was conducted to
determine the predictive ability of each variable separately. Then,
variables with a $P < 0.1$ were entered into multiple logistic regression
analysis adjusted by the demographic and clinical variables. Odds ratios
(OR) and 95% confidence intervals (CI) were calculated for each regres-
sion analysis. Furthermore, in order to have a comprehensive as-
essment of the two patient groups, a series of independent $t$-tests were
done to allow between-group comparisons of fallers and non-fallers on
all outcome measures of this study. All analyses were conducted using
the IBM SPSS statistics software (Version 22). Significance level was set
at $P < 0.05$.

3. Results

3.1. Participants and fall data

Approximately 43% of participants (30 patients) reported 1 or more
falls during the 6-month follow-up period. Table 1 summarizes parti-
cipants’ characteristics including clinical and demographic data for the
two patient groups (non-fallers and fallers). The results of a series of
independent $t$-tests revealed that there were significant differences in

<table>
<thead>
<tr>
<th>Predictors</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>$P$-value</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_s$</td>
<td>0.903</td>
<td>0.294</td>
<td>9.419</td>
<td>1</td>
<td>0.002</td>
<td>2.466 (1.386–4.389)</td>
</tr>
<tr>
<td>$\lambda_l$</td>
<td>0.638</td>
<td>0.271</td>
<td>5.548</td>
<td>1</td>
<td>0.018</td>
<td>1.893 (1.113–3.219)</td>
</tr>
</tbody>
</table>

Table 2

Univariate logistic regression analysis with fall incidence (no fall versus ≥1 fall) as the dependent variable.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>$P$-value</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_s$</td>
<td>0.524</td>
<td>0.265</td>
<td>3.925</td>
<td>1</td>
<td>0.048</td>
<td>1.689 (1.006–2.837)</td>
</tr>
<tr>
<td>$\lambda_l$</td>
<td>0.315</td>
<td>0.249</td>
<td>1.606</td>
<td>1</td>
<td>0.205</td>
<td>1.081 (0.842–1.421)</td>
</tr>
<tr>
<td>$\lambda_s$</td>
<td>0.284</td>
<td>0.259</td>
<td>1.208</td>
<td>1</td>
<td>0.222</td>
<td>1.329 (0.800–2.206)</td>
</tr>
<tr>
<td>$\lambda_l$</td>
<td>0.345</td>
<td>0.277</td>
<td>1.552</td>
<td>1</td>
<td>0.223</td>
<td>1.412 (0.821–2.429)</td>
</tr>
</tbody>
</table>

The results of the univariate logistic regression models revealed that
$\lambda_s$ under both the single and dual-task conditions and $\lambda_l$ under
the single task condition were the significant fall predictors in PwMS, while
DTC of $\lambda_s$ and $\lambda_l$ were not significant predictors (Table 2). Since there
were significant differences between fallers and non-fallers regarding
disability, gender and BMI, we conducted multiple regression analysis
and adjusted the effects of these variables. The results of multiple re-
gression analysis revealed that only $\lambda_s$ was the significant fall predictor
i.e. the odds of falling was 2.21 times greater with 1 standard deviation
(SD) increase in the $\lambda_s$ (Table 3). In addition, the results of series of
independent $t$-tests revealed that fallers had greater instability in
walking, as determined by $\lambda_s$, $\lambda_l$ and cognitive $\lambda_s$ than non-fallers at
the time of assessment (Table 4).

4. Discussion

In the present study, we investigated the predictive ability of LDS
for future fall identification in a sample of PwMS, who were ambulatory
independent. In our sample, 43% of participants experienced at least
one fall over the 6-month follow-up period and were classified as
fallers. The results of the logistic regression analysis, after adjusting for
clinical and demographic variables, revealed that short-term LyE ($\lambda_s$)
under the single-task condition was the significant fall predictor in
PwMS. i.e. reduced LDS of walking at the time of assessment was pre-
dictive of future falls. This finding is novel and significant as this was
the first prospective study that investigated the predictive ability of a
non-linear measure of gait stability (LyE) in PwMS. Although both
groups of fallers and non-fallers were ambulatory with mild-to-moder-
ate disease severity (EDSS < 6) and had similar ages and disease
duration, they had distinct levels of gait LDS which may provide an
insight into a mobility-related factor associated with falling in these
patients. This finding supports the results of previous studies in the
healthy elderly which demonstrated that LyE may be a valid predictor
of falling (Lockhart and Liu, 2008; Toebes et al., 2012; van Schooten
et al., 2011).
environments (narrow-based walking) may provide additional insight into demanding tasks (serial seven subtraction) in the more challenging en- the previous experiments. Maybe, the use of more attentional de- versus treadmill walking) or the level of cognitive task difficulty used in previous studies regarding dual tasking may be due to differences in the variability with healthy controls (Fino, 2016). However, in this study during dual-task walking despite similar single-task stability and significant decrease in the LDS and an increase in stride time variability.

Among the variables investigated in this study, the LDS measures in the dual-task condition and their DTCs were not predictive of the future falls in PwMS. Although there was significant between-group differences in the dual-task test variables, in terms of prediction and after the dual-task condition and their DTCs were not predictive of the future falls in PwMS (Bruijn et al., 2010). Furthermore, patients of this study were assessed with a laboratory-based set-up including a motion analysis system and a treadmill. The use of wireless trunk accelerometers during over ground walking in daily life may enhance the assessment of LDS in the real life situations or in the clinical settings (van Schooten et al., 2016). In addition, they seem to be more time efficient than laboratory-based measurements. Future studies shall utilize three dimensional trunk accelerometers to investigate the predictive validity of a series of nonlinear measures, combined with subjective measures (Tajali et al., 2017), in a larger sample of MS patients to develop an optimal model to predict the fall risks associated with walking.

5. Conclusion

In conclusion, this study supports using the LDS to predict the probability of falling in PwMS, thereby incorporating it into the fall risk assessments and fall prediction models. As the reduced ability to re- spond effectively to intrinsic or small extrinsic perturbations during walking can predispose patients to larger perturbations and to falling (Pai et al., 2014a), investigation of the effects of perturbation-based gait rehabilitation programs on the rate of falling is recommended in these patients (Pai et al., 2014b). This issue is important as the results of previous studies revealed that traditional fall prevention programs including stretching, strengthening, yoga and balance training were not effective in reducing the rate of future falling in PwMS (Gunn et al., 2015).

Declaration of Competing Interest

None of the authors had any financial or other interests relating to the manuscript to be submitted for publication in the journal of clinical biomechanics.

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References


From a methodological perspective, we measured long-term LDS in a shorter time interval (one stride versus 4–10 stride). The logic behind this analysis was the fact that previous studies that measured λ_s in 4–10 stride did not reveal any sensitivity to between-group differences for this variable (Dingwell et al., 2001; Dingwell and Marin, 2006). We hypothesized that this may be due to the fact that λ_s is measured in an interval where most divergence is damped down due to either explicit control and/or the attractor size limitations (physiological or anato- mical constraints). In fact, we again found a predictive ability only for the short-term LDS not the long-term. Therefore, short- term LDS seems to be a more valid indicator to estimate the probability of falling in PwMS (Bruijn et al., 2010).

Although this study highlighted an association between a decreased dynamic stability and an increased fall risk in PwMS, several limitations are needed to be considered. Firstly, the fall incidence in our sample was less than what is commonly reported in the literature (< 50%) (Gianni et al., 2014; Gunn et al., 2013a), which may affect the results of this study. Secondly, the method of this study cannot be applied to very poor walkers and hence the applicability is limited to a subset of pa- tients with an independent walking ability. Furthermore, patients of this study were assessed with a laboratory-based set-up including a motion analysis system and a treadmill. The use of wireless trunk accelerometers during overground walking in daily life may enhance the assessment of LDS in the real life situations or in the clinical settings (van Schooten et al., 2016). In addition, they seem to be more time efficient than laboratory-based measurements. Future studies shall utilize three dimensional trunk accelerometers to investigate the pre- dictive validity of a series of nonlinear measures, combined with subjective measures (Tajali et al., 2017), in a larger sample of MS patients to develop an optimal model to predict the fall risks associated with walking.

Table 4:

\[
\begin{array}{cccc}
\text{Variables} & \text{Non-fallers} & \text{Fallers} & \text{P-value} \\
\text{Mean (SD) (n = 40)} & \text{Mean (SD) (n = 30)} & \\
\lambda_s & 0.537 (0.133) & 0.668 (0.177) & 0.001 \\
\lambda_l & 0.332 (0.198) & 0.407 (0.107) & 0.013 \\
\text{Cognitive } \lambda_s & 0.521 (0.139) & 0.600 (0.176) & 0.041 \\
\text{Cognitive } \lambda_l & 0.342 (0.142) & 0.385 (0.138) & 0.204 \\
\text{DTC } \lambda_s & 0.009 (0.200) & 0.059 (0.162) & 0.272 \\
\text{DTC } \lambda_l & -0.051 (0.358) & 0.039 (0.177) & 0.207 \\
\end{array}
\]

\(\lambda_s\): Lyapunov exponent (LyE) over the duration of one step, \(\lambda_l\): LyE over the duration of one stride, cognitive \(\lambda_s\): LyE in the dual task condition over the duration of one step; DTC: dual task cost.

There is an increasing evidence that LDS could be used as a perti- nent bio-marker for identifying various diseases and adverse conditions such as falling and disability (Reynard et al., 2014; Stergiou and Decker, 2011; Toebes et al., 2012). Consistent with this hypothesis, in a cross sectional study, Huisinga et al., found that trunk control during walking was impaired in PwMS in comparison to the healthy subjects suggesting that improving trunk stability should be considered as a goal in the balance rehabilitation protocols (Huisinga et al., 2013). Fur- thermore, Peebles et al. found differences in the LDS between PwMS who had a previous fall history and those who had no fall history (Peebles et al., 2017). Although the results obtained in the aforementioned study are valuable in terms of investigating a series of nonlinear and linear gait variability and stability measures in PwMS (Peebles et al., 2017), they relied on retrospective fall assessment and the pre- dictive values of these parameters to identify fall risk remained unknown. Another noteworthy study by van Schooten et al. illustrated that daily life gait characteristics including LDS were predictive of future falls in the elderly (van Schooten et al., 2016). In contrast to our study, they used a single trunk accelerometer and analyzed a series of motor control characteristics including gait stability, variability, smoothness and symmetry in the older adults (van Schooten et al., 2016). Taken together, these findings revealed that investigation of parameters related to locomotor control may be a promising approach to identify patients who require gait retraining in their fall prevention programs (Hilifker et al., 2013; van Schooten et al., 2016).

Among the variables investigated in this study, the LDS measures in the dual-task condition and their DTCs were not predictive of the future falls in PwMS. Although there was significant between-group differences in the dual-task test variables, in terms of prediction and after the adjustment of disability, gender, and BMI; these variable did not yield to a significant prediction. Regarding the predictive validity of DTC of laboratory gait measures, only the DTC of traditional gait parameters including gait speed and stride length were investigated previously in PwMS (Etemadi, 2016). In a study by Etemadi, gait was assessed through an electronic walkway and only the DTC of walking speed was found to be predictive of the future falls in PwMS (Etemadi, 2016). Regarding other patient’s populations, in a longitudinal study by Fino, the effect of dual taking on the LDS of walking was assessed in 5 pa- tients with cerebral concussion (Fino, 2016). The results revealed a significant decrease in the LDS and an increase in stride time variability during dual-task walking despite similar single-task stability and variability with healthy controls (Fino, 2016). However, in this study no association between DTC of LDS and falling was investigated. Overall, the controversy obtained in the results of our study with previous studies regarding dual tasking may be due to differences in the study design, study variables, experimental conditions (over ground versus treadmill walking) or the level of cognitive task difficulty used in the previous experiments. Maybe, the use of more attentional de- manding tasks (serial seven subtraction) in the more challenging en- vironments (narrow-based walking) may provide additional insight into

References


