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Letter to the Editor

Gait stability in patients treated by fingolimod: A longitudinal pilot study on 9 patients with multiple sclerosis

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Dear Editor,

1. Introduction

Walking difficulties are reported by > 85% of patients with multiple sclerosis (MS), even in the initial stages of the disease [1]. The use of quantitative gait analysis for measuring stride time variability (STV) – a marker of gait stability [2] – reveals very subtle gait deficits. STV also represents an interesting predictor of falls in MS patients, even better than the EDSS [3]. The use of dual tasking – the ability to simultaneously perform a cognitive task while walking (i.e. walking while talking) [4] – allows an access to the higher level of gait control [5]. Fingolimod, an oral disease-modifying treatment, reduces the relapse rate and may reduce the MS-related disability [6]. However, the impact of fingolimod on subtle gait changes, such as STV, has never been studied. This longitudinal pilot study aims to investigate the effects of fingolimod on STV during single and dual-task conditions in 9 MS patients after at least one year of treatment.

2. Methods

Nine outpatients with relapsing-remitting MS (mean age: 42.2 ± 4.3 years; 56% female; mean EDSS 2.4 ± 1.8; mean disease duration: 80.6 ± 64.1 months) were included in this prospective study at treatment initiation with fingolimod and after at least one year of continuous treatment (mean interval: 504 ± 180 days). Study procedures have been previously described [7]. Briefly, inclusion criteria were: a confirmed diagnosis of relapsing-remitting multiple sclerosis according to the revised McDonald's criteria [8], an ability to walk without any assistance, an absence of other neurological or orthopedic conditions interfering with gait, a treatment with fingolimod (0.5 mg daily). During both evaluations (baseline and one-year), all patients were stable (without any relapse within 60 days or corticosteroid treatment within 30 days prior the evaluation); patients were not excluded if they presented any relapse between both evaluations. Patients were asked to walk at self-selected and comfortable pace on a straight line of 10 m. To measure the higher levels of gait control, we included four dual task conditions that were performed in a random order and without any task prioritization: forward counting, backward counting, semantic fluency (generation of animal names) and phonemic fluency (generation of words starting with letter P). Spatiotemporal gait parameters (i.e., STV, walking speed, stride length and cadence) were computed using the trajectories of heel marker reconstructed with a 12-camera optoelectronic system (Vicon Mx3 +, Vicon Peak) synchronized with footswitches (Aurion Zerowire) and computed with MatLab 2012b (MathWorks, Natick, MA). The main outcome variable was STV, calculated according to the formula: STV = [(standard deviation of stride time) / (mean value of stride time)] * 100 (%). Comparisons between baseline and after at least 1-year assessments were performed with Wilcoxon Signed-Rank test. P-values < 0.05 were considered as significant. A post-hoc power analysis with an alpha set at 0.05 and a power set at 80% were applied to compute the number of patients needed to obtain a significant p-value when comparing our main outcome (STV) at baseline and at 1-year assessment. All data were analyzed with SPSS version 23 (SPSS Inc., Chicago, Illinois, USA). The research protocol was approved by the Geneva University Hospitals institutional review board, and informed consent was obtained from all patients.

3. Results

Spatiotemporal gait parameters while single and dual tasking are presented in Table 1.

The main outcome and other spatiotemporal gait parameters were not significantly different between STV at baseline and after at least one year of treatment in single walking task, as well as in each dual task. The power analysis shows that 1234 MS patients would be needed to be included to reach statistical significance for STV between baseline and 1-year assessment. That confirms that STV is stable after one year of well-conducted fingolimod treatment.

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Table 1
Comparison of gait performances between baseline and after at least 1 year (n = 9).

	Baseline	One year	p-value*
Single task			
STV, %	2.12 ± 1.53	2.28 ± 1.55	0.767
Walking speed, mean (m/s)	1.23 ± 0.32	1.22 ± 0.33	0.678
Cadence, mean (steps/min)	108.57 ± 8.04	109.05 ± 8.40	0.594
Stride length, mean (m)	1.35 ± 0.30	1.32 ± 0.31	0.051
Dual tasks			
Forward counting			
STV, %	3.42 ± 2.27	2.32 ± 1.36	0.139
Walking speed, mean (m/s)	1.21 ± 0.30	1.13 ± 0.35	0.110
Cadence, mean (steps/min)	106.24 ± 8.76	103.00 ± 14.47	0.441
Stride length, mean (m)	1.36 ± 0.29	1.29 ± 0.29	0.066
Backward counting			
STV, %	4.83 ± 7.69	4.05 ± 4.65	0.594
Walking speed, mean (m/s)	1.13 ± 0.32	1.11 ± 0.41	0.515
Cadence, mean (steps/min)	102.67 ± 13.47	99.79 ± 18.84	0.314
Stride length, mean (m)	1.31 ± 0.30	1.28 ± 0.34	0.441
Semantic fluency			
STV, %	4.13 ± 4.17	3.45 ± 4.50	0.859
Walking speed, mean (m/s)	1.01 ± 0.33	0.96 ± 0.38	0.314
Cadence, mean (steps/min)	94.90 ± 17.93	90.56 ± 22.86	0.139
Stride length, mean (m)	1.25 ± 0.27	1.21 ± 0.32	0.214
Phonemic fluency			
STV, %	5.23 ± 3.69	7.91 ± 12.07	0.953
Walking speed, mean (m/s)	0.97 ± 0.28	0.88 ± 0.38	0.110
Cadence, mean (steps/min)	93.80 ± 15.22	85.41 ± 27.74	0.173
Stride length, mean (m)	1.23 ± 0.28	1.18 ± 0.28	0.214

STV = stride time variability (coefficient of variation of stride time).
* Comparison based on Wilcoxon signed-rank test.

4. Discussion

This pilot study showed a non-significant difference in STV between baseline and after at least one year in fingolimod-treated patients in single and dual tasks conditions. MS patients are likely to experiment deficits in both cognitive and motor components due to progression of the disease: previous reports showed a progressive deterioration of gait in patients with MS [9]. In this study, the use of quantitative gait analysis, focusing specifically on STV while single and dual tasking, confirms an absence of any subtle gait deterioration in MS patients treated with fingolimod. This absence of deterioration in STV may also suggest an absence of progression of falls risk, as STV has been identified as a reliable marker of future falls [3]. The four cognitive tasks used in this pilot study refer to cognitive functions related to attention (forward counting), working memory (backward counting) and executive functions (semantic and phonemic verbal fluency) [10]. These various cognitive domains stressed while walking (i.e. dual task), remained also unchanged after one year of treatment. Similarly, this increased cognitive load due to a concurrent cognitive task did not significantly modify STV after one year, also suggesting an absence of deterioration of the cognitive components of gait control. Similar STV stability while single and dual tasking has been reported with patients treated by natalizumab [7].

This pilot study provides promising findings about the absence of gait deterioration in fingolimod-treated patients; however, several limitations must be considered. First, the small sample size should lead to further research including a greater number of subjects. Secondly, although we tried to keep the same time interval of at least one year, the period between both gait assessments was still variable. Third, a one year follow-up may not be sufficient to demonstrate a sustained effect of the medication on gait stability; however, we used a very sensitive approach to detect subtle gait changes, such as measuring STV while single and dual tasking [4]. Fourth, including a measure of single walking task at fastest walking speed would have been of interest, as absolute values of within-day variability have been demonstrated as invariant during walking test performed at fastest walking speed [11]. These findings need to be confirmed in a larger cohort and compared with other disease modifying therapies.

Conflict of interest

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