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Gait quality and function after fampridine treatment in patients with multiple sclerosis – A prospective cohort study

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ABSTRACT

Background: Fampridine has shown to improve walking speed, motor control, and balance in patients with multiple sclerosis. However, potential fampridine-induced changes in gait quality and underlying mechanisms, evaluated by three-dimensional gait analysis, are poorly examined.
The aim was to examine if two weeks of fampridine treatment would improve gait quality (using Gait Profile Score and Gait Variable Scores from three-dimensional gait analysis) and gait function (using performance-based tests, spatiotemporal parameters, and self-perceived gait function).
Methods: 14 participants with multiple sclerosis were included (9 women and 5 men, age 53.6 ± 12.8 years, disease duration 21 ± 9.1 years) in this cohort study. Tests were completed prior to fampridine and after 14 (± 1) days of treatment. Three-dimensional gait analyses were completed, and kinematic measures were calculated for overall gait quality using Gait Profile Score, and for joint-specific variables, Gait Variable Scores. Gait function was assessed using spatiotemporal parameters, performance-based tests, and a patient-reported outcome measure. Student's paired *t*-test/Wilcoxon signed rank test were used to compare baseline and follow-up variables. Sample size calculation for Gait Profile Score required at least 9 participants.
Findings: No fampridine-induced improvements in gait quality were demonstrated. For gait function, improvements were found in performance-based tests (*Timed 25-Foot Walk*: −11.5%; *Six Spot Step Test*: −13.9%; *2-Minute Walk Test*: 18.2%) and self-perceived gait function (*12-item*MS *Walking Scale:* –35.2%).
Interpretation: Although two weeks of fampridine treatment in patients with multiple sclerosis improved gait function, there was no change in overall kinematic quality of gait.
Trial registration:
This work was collected as a part of a registered clinical trial (MUST): ClinicalTrials.gov NCT03847545

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease of the central nervous system and the most frequent neurological disease affecting young adults (Filippi et al., 2018). MS causes a variety of clinical manifestations including muscle weakness, spasticity, paresis, and sensory deficits (Pau et al., 2014), resulting in functional limitations such as reduced walking speed, endurance, and poor balance. Gait limitations is a main cause of disability in patients with MS (Larocca, 2011), and up to 76% of patients require a walking aid or wheelchair at

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some stage (Kister et al., 2013).

Fampridine is presently the only medical drug used to alleviate gait function in MS (Ahdab et al., 2019). It enhances signal conduction in demyelinated axons by blocking voltage-dependent potassium channels (Hayes, 2007). Clinical studies demonstrate improved walking speed (Filli et al., 2018; Goodman et al., 2010; Jensen et al., 2014; Zörner et al., 2016), walking endurance (Filli et al., 2018; Zörner et al., 2016), coordination (Jensen et al., 2014; Jensen et al., 2016), balance (Hupperts et al., 2016; Jensen et al., 2014), self-perceived gait function (Goodman et al., 2009; Hupperts et al., 2016), and Functional Ambulation Profile (FAP) Score (Allart et al., 2015; Rodriguez-Leal et al., 2018) (a composite value of selected spatiotemporal parameters) (Givon et al., 2009) in a subset of patients with MS. However, the effect of fampridine on neuromechanical changes of gait, including the overall 'quality of gait', in patients with MS has not been examined.

Three-dimensional gait analysis (3DGA) is an established method for objective quantification of kinematic, kinetic, and spatiotemporal parameters (Benedetti et al., 1999; Martin et al., 2006) and is considered the gold standard for gait analysis (Cameron and Wagner, 2011). The Gait Profile Score (GPS) is a summary measure of 3DGA that evaluates the overall quality of gait by comparing nine kinematic variables, described as Gait Variable Scores (GVS), relative to normative data. A higher GPS/GVS implies a larger deviation from a hypothetical "normal" gait and a greater level of impairment (Baker et al., 2009). GPS and/or GVS have been applied in previous studies involving patients with MS (Andreopoulou et al., 2019; Coghe et al., 2015; Morel et al., 2017; Pau et al., 2014; Pau et al., 2018) and are considered feasible, reliable (Andreopoulou et al., 2019; Pau et al., 2014), and responsive in this population (Pau et al., 2014).

The literature on fampridine-induced 3DGA changes in patients with MS, only include two publications on the same study: One demonstrating changes on kinematic variables (Zörner et al., 2016) and one on kinetic variables (Weller et al., 2020). The study however, was performed during treadmill walking and the analysis included only a few kinematic variables, thus not allowing an interpretation of overall kinematic quality of gait (Zörner et al., 2016). The use of GPS/GVS, in combination with performance-based tests and self-perceived gait function, may help evaluate neuromechanical changes of fampridine on overall quality of gait.

The aims of this study were to test the hypothesis that both gait quality (using GPS based on nine different GVS readings) and gait function (using performance-based tests, spatiotemporal variables, and self-perceived gait function) would improve in patients with MS after two weeks of fampridine treatment. Further, we hypothesized that changes in GPS would be associated with changes in performance-based tests and self-perceived gait function.

2. Methods

2.1. Participants and setting

The present cohort study (without a separate control group) is part of a larger explorative, prospective observational cohort study (the MUST study) conducted at Odense University Hospital, Denmark from December 2018 to October 2021, in which participants were offered fampridine in a start-up period before evaluating its potential clinical impact. Therefore, the current sample includes both fampridine responders and non-responders (Trial registration: ClinicalTrials.gov NCT03847545). Data for the current sub-study were collected between May 2019 and May 2021 and are reported here according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (Vandenbroucke et al., 2007). The study was approved by the National Committee on Health Research Ethics (S-20170203) and the Danish Data Protection Agency (2012-58-0018) and was conducted in accordance with the Declaration of Helsinki. Prior to testing, participants received oral and written information about the study and provided written informed consent.

Eligible participants were recruited from the outpatient MS Clinic at Odense University Hospital. Inclusion criteria were a diagnosis of MS according to the McDonald 2010 criteria (Polman et al., 2011), age > 18 years, and an Expanded Disability Status Score (EDSS) between 4 and 7. Finally, participants should comply with clinical guidelines for receiving fampridine based on clinical symptoms and neurological evaluations. Exclusion criteria were history of epilepsy, MS attacks or acute decrease of functional capacity within 60 days, change in immunomodulatory treatment within 60 days, cancer within five years, clinically significant systemic disease, concomitant treatment with cimetidine, carvedilol, propranolol or metformin, and previous operations in the back or lower extremities.

The participants included in the MUST study were randomly allocated to the present sub-study involving 3DGA (computerised at a sequence of 1:1) resulting in an extra test day at the test-site for each visit. The randomization procedure was done to reduce the number of time-consuming procedures and adhere to the sample size calculation (Section 2.3). Assessments were performed at baseline (T_0), prior to starting fampridine, and at follow-up (T_1) after 14 ($\pm$1) days of 10 mg fampridine® (Biogen, Cambridge, MA, USA) twice daily. Both T_0 and T_1 consisted of two consecutive days, one including the performance-based tests and one including 3DGA. Walking aids were used as required and kept identical for the individual tests at T_0 and T_1. At T_0 baseline characteristics was collected, including age, gender, height and weight (from which Body Mass Index (BMI) was calculated), disease duration, and EDSS.

2.2. Outcome measures

2.2.1. Gait quality using 3D gait analysis

Kinematic data were acquired using a Vicon T40 motion analysis system (Vicon, Oxford, UK) consisting of eight cameras sampling at 100 Hz. Prior to testing, relevant anthropometric measures were collected for the individual participant, followed by montage of 24 reflective markers and estimation of joint angles based on the modified Plug-In Gait model (Davis et al., 1991).

Participants walked barefooted at their normal self-selected walking speed, but were asked to adjust this at the follow-up visit if the self-selected walking-speed exceeded $\pm$5% difference between the two visits. Data from five full gait cycles (unilateral heel-strike to heel-strike) for the dominant side (allowing suitable rest time between trials) at each visit were used for analyses. One assessor with 5 years of experience with this method (first study author) was responsible for marker placement, collecting the gait data, and data processing.

Both GPS and the nine individual GVS were used to evaluate gait quality and potential kinematic changes at joint level, respectively according to Baker et al. 2009 (Baker et al., 2009). GPS is the root mean square (RMS) difference between the data of relevant kinematic variables of an individual participant and the averaged data from a reference group comprised of people without gait limitations. GVS refers to the RMS difference of the kinematic variables at each joint level: pelvic tilt, obliquity and rotation; hip flexion-extension, adduction-abduction, and rotation; knee flexion-extension; ankle dorsiflexion; and foot progression (Baker et al., 2009). For normative data, we used an age-matched reference group collected in our own lab (n: 29; Gender: 14 men/15 woman, age (mean (SD)): 50.5 years (10.3); BMI: 25.1 (3.0)).

We processed the raw data using used Vicon Nexus Software (version 2.9.2 or later) and Vicon Polygon Software (version 4.4.5 or later) and subsequently analysed GPS and GVS using a custom-made MatLab script.

2.2.2. Gait function

Gait function was evaluated using spatiotemporal parameters captured during the 3DGA, performance-based tests, and a patient-reported measure. The Timed 25-Foot Walk (T25FW) measures short-

distance walking speed and was performed according to the Multiple Sclerosis Functional Composite (Fischer et al., 2001). The Six Spot Step Test (SSST) evaluates ambulatory function and involves criss-cross walking across a rectangular course as quickly as possible while kicking five blocks out of circles marked on the floor (Nieuwenhuis et al., 2006). In the 2-min Walk Test (2MWT) (Gijbels et al., 2011), participants walked laps on a 20-m lane for 2 min, and the total distance travelled was recorded. Self-perceived impact of MS on gait function was measured using the 12-item MS Walking Scale (MSWS-12), a questionnaire evaluating gait limitations due to MS during the past two weeks (Hobart et al., 2003). All included measuring tools are considered reliable and valid for the current patient group (Callesen et al., 2019; Gijbels et al., 2011; Motl et al., 2017; Pilutti et al., 2013; Scalzitti et al., 2018).

2.3. Statistical analysis

Statistical analyses were performed using Stata/BE 17.0 (StataCorp LLC, College Station, TX, USA).

Sample size calculation for the present analysis was performed a priori using previously reported GPS values on a comparable MS population (GPS mean ± SD) 9.1° ± 1.3° (Andreopoulou et al., 2019) and a minimal clinically important difference of 1.6° GPS, originally defined in a sample of children (Baker et al., 2012). As no SD was reported for the original paper, we generalised the between-individual SD to the standard deviation of the change scores as SD = 1.3°. Based on a paired design, alpha = 0.05, 80% statistical power, assumption of Gaussian distribution of change scores, and attainment of minimal clinically important difference, a minimum of 9 participants were needed to reject the null hypothesis of no change from T_0 to T_1.

Gaussian distribution for included data was investigated using normal probability plots and the Shapiro-Wilk test. To investigate changes between T_0 and T_1, we used Student's paired *t*-test with 95% confidence intervals (parametric) and Wilcoxon signed rank test with median values and bootstrap confidence intervals (95% BCa) (non-parametric).

To compare characteristics of the included participants with MS to, those of the patients who were randomized to perform 3DGA but declined, we used Student's unpaired *t*-test (parametric) and Wilcoxon rank sum test (non-parametric).

Due to the small sample size, we had no hypothesis for the specific form of association between GPS change scores and change scores of the performance-based measures and self-perceived gait function. Therefore, both Pearson's product-moment correlation coefficient r and Spearman's rank-order correlation coefficient ρ (rho) are reported. For kinematic and spatiotemporal data, the results for the dominant side are reported.

3. Results

Of the 71 patients with MS invited to participate in the larger cohort study (MUST), 16 declined. During the screening process, further 8 patients did not meet inclusion criteria. Of the remaining 47 participants, 26 were randomly allocated to 3DGA and 14 of these accepted the extra visit associated with the 3DGA; these 14 participants were included in the current sub-study (Fig. 1). No differences in characteristics were detected between the 14 included participants and the 12 patients who were randomized to 3DGA but declined (Table 1). All included participants completed both visits. The average age was 54 years, the majority were women, were overweight, and had an EDSS score between 4 and 6. The proportion using a walking aid during testing varied from 21% to 43% (Table 1).

We found no improvements in gait quality in terms of GPS or any

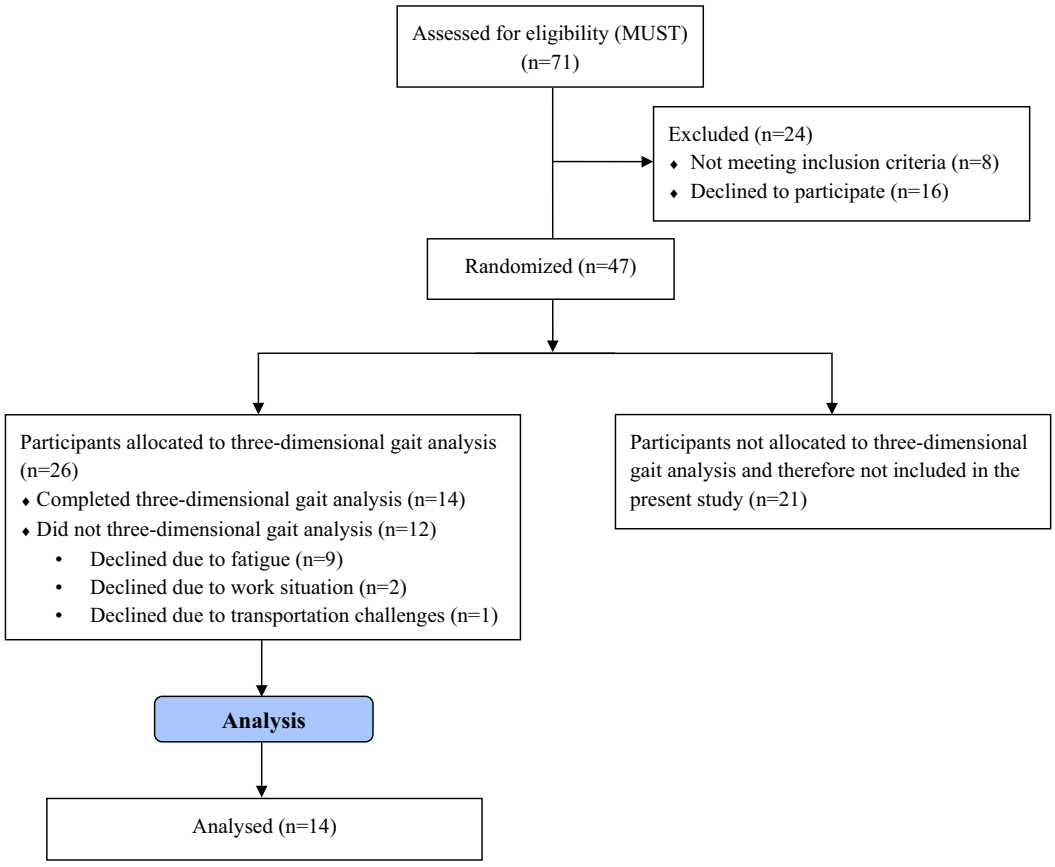

Fig. 1. Flowchart.
Illustration of the inclusion and the progress of all participants for the current sub-study on three-dimensional gait analysis (3DGA).

Table 1
Baseline characteristics of included participants and patients that declined to perform 3DGA.

Characteristics	Performed 3DGA *(n = 14)*	Declined 3DGA *(n = 12)*	*p*-value
Age, years	53.6 (12.8)	58.7 (12.9)	0.18
Females, n (%)	9 (64)	6 (50)	1.00
BMI, kg/m^2	26.2 (3.9)	NA	NA
Disease duration, years	21 (9.1)	20.8 (10.1)	0.95
EDSS	5.2 (0.8)	5.6 (0.9)	0.43
Patients using walking aids during tests, n (%):			
3DGA	4 (28.6)	NA	NA
T25FW	3 (21.4)	4 (33.3)	0.53
SSST	3 (21.4)	5 (41.7)	0.27
2MWT	6 (42.9)	6 (50.0)	0.73

Values are reported as mean (SD) or n (%).
3DGA: Three-dimensional gait analysis; EDSS: Expanded Disability Status Score; T25FW: Timed 25-Foot Walk; SSST: Six Spot Step Test; 2MWT: 2-min Walk Test; NA; not applicable.

kinematic changes at joint level by means of GVS ($p > 0.05$), following two weeks of fampridine treatment (Table 2a). However, we found significant improvement of gait function according to performance-based tests: T25FW, SSST, and 2MWT ($p < 0.003$) and self-perceived gait function: MSWS-12 ($p < 0.001$) (Table 2b). No significant changes were seen in the spatiotemporal parameters ($p > 0.05$) (Table 2b).

No significant correlations were detected between change in GPS and changes in the performance-based tests or self-perceived gait function ($p > 0.05$), see Fig. 2.

4. Discussion

4.1. Main findings

This is the first study examining potential fampridine-induced improvements in gait quality using a gait summary measure in patients with MS. The study represents a pragmatic clinical approach where participants were offered fampridine in a start-up period before evaluating its potential clinical impact. Therefore, the current study represents a sample including both fampridine responders and non-responders. Contrary to our hypothesis, we found no significant group mean improvements in gait quality and joint specific kinematic scores following fampridine treatment. However, improvements in the performance-based tests and self-perceived gait function confirmed our hypothesis of improved gait function. We found no significant associations between gait quality (GPS) and measures of gait function, consequently rejecting our hypothesis. Fampridine-induced changes thus appear to be restricted to performance-based gait variables and self-perceived gait function. As the underlying neuromechanical joint specific kinematic deviations (GVS) and overall quality of gait (GPS) showed no difference, the walking strategy remains unaltered i.e. MS-related gait limitations remain unchanged despite better function after two weeks of fampridine treatment.

4.2. Quality of gait

Compared to a median GPS of 4.8° in our age-matched reference group (data not shown), the participants with MS in the present study showed impaired gait quality at baseline, with a median GPS of 9.39° (IQR: 8.30°/9.82°), which is comparable with a GPS of 9.1° reported in a previous study on patients with MS (Andreopoulou et al., 2019). Thus,

Table 2a
Gait quality at baseline (T_0) and 14-day follow-up (T_1) for 14 patients with multiple sclerosis.

Gait quality variables	T_0	T_1	Change [95% CI]	% change	*p*-value
Overall GPS (degrees)	8.50 (7.61/8.96)	7.90 (7.39/9.35)	−0.21 [−0.72; 0.29]	−2.47	0.456
GVS – dominant side (degrees)					
Pelvic tilt	3.82 (2.71/7.10)	5.24 (3.34/6.23)	0.06[−1.35; 1.46]	1.57	0.931
Pelvic obliquity	2.24 (1.85/2.76)	2.05 (1.37/2.39)	−0.22 [−0.49; 0.04]	−9.82	0.094
Pelvic rotation	4.45 (3.70/5.76)	5.38 (3.95/5.98)	0.22 [−0.43; 0.86]	4.94	0.482
Hip flexion-extension	9.18 (8.08/11.87)	9.47 (7.69/12.74)	0.31[−0.80; 1.42]	3.38	0.561
Hip abduction-adduction	4.38 (3.41/4.95)	4.15 (2.71/5.24)	−0.22 [−0.80; 0.35]	−5.02	0.410
Hip rotation	7.89 (6.32/11.82)	7.11 (5.61/9.57)	−1.03 [−3.16; 1.10]	−13.05	0.316
Knee flexion-extension	13.25 (10.80/14.86)	12.28 (8.38/15.03)	−0.99 [−2.14; 0.17]	−7.47	0.087
Ankle dorsi flexion	8.88 (7.08/10.23)	8.68 (6.64/10.75)	−0.30 [−1.09; 1.01]*	−3.38	0.510
Foot progression	7.36 (5.12/8.50)	6.96 (6.20/9.32)	0.25 [−0.91; 1.41]	3.40	0.648

Table 2b
Gait function at baseline (T_0) and 14-day follow-up (T_1) for 14 patients with multiple sclerosis.

Gait function variables	T_0	T_1	Change [95% CI]	% change	*p*-value
Performance-based test and PROM					
T25FW (s)	6.30 (5.35/7.05)	5.58 (4.55/6.50)	−0.82 [−1.16; −0.47]	−11.51	**<0.001**
SSST (s)	11.87 (3.87)	10.22 (2.75)	−1.65 [−2.65; −0.49]*	−13.90	**0.002**
2MWT (m)	126.80 (25.71)	149.84 (36.98)	23.04 [14.03; 28.00]*	18.17	**0.001**
MSWS-12 (points)	63.84 (13.44)	41.37 (18.69)	−22.47 [−29.17; −4.17]*	−35.17	**<0.001**
Spatiotemporal parameters – dominant side					
Walking speed (m/s)	0.94 (0.20)	0.94 (0.19)	0.00 [−0.01; 0.02]	0.00	0.664
Cadence (steps/min)	105.17 (8.90)	104.35 (9.48)	−0.82 [−2.50; 0.86]	−0.78	0.311
Step length (m)	0.54 (0.08)	0.55 (0.08)	0.01 [−0.00; 0.03]	1.85	0.113
Step width (m)	0.17 (0.04)	0.17 (0.04)	0.00 [−0.01; 0.01]	0.00	0.874
Stride length (m)	1.07 (0.16)	1.08 (0.16)	0.02 [−0.01; 0.04]	0.93	0.160

Values at T_0 and T_1 are mean (SD) or median (IQR). Change scores are mean [95% CI] if normally distributed or median [95% BCa] (followed by *) if non-normally distributed.
GPS: Gait Profile Score; GVS: Gait Variable Scores; T25FW: Timed 25-Foot Walk; SSST: Six Spot Step Test; 2MWT: 2-min Walk Test; MSWS-12: 12-item MS Walking Scale; IQR: interquartile range; SD: standard deviation.

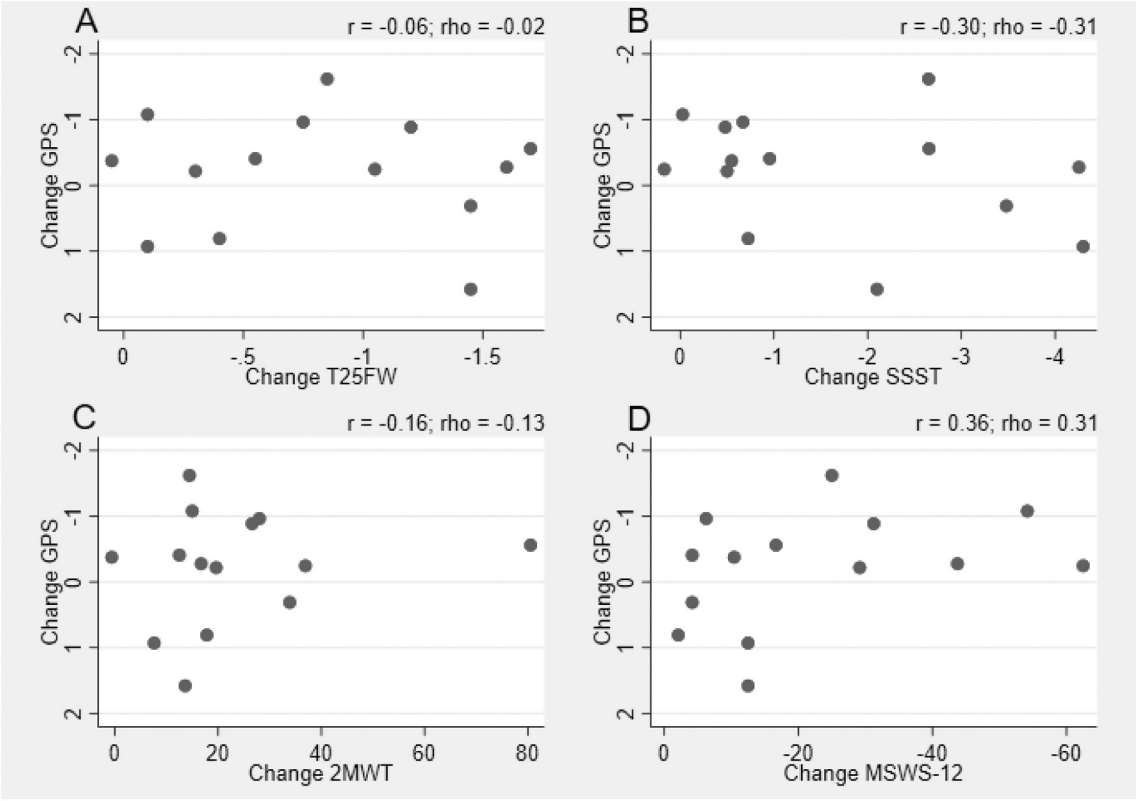

Fig. 2. Scatterplots of associations.
Scatterplots of associations between change in GPS and change in (A) T25FW, (B) SSST, (C) 2MWT and (D) MSWS-12 for 14 patients with multiple sclerosis.
r: Pearson correlation coefficient; rho: Spearman's rank correlation coefficient; GPS: Gait Profile Score; T25FW: Timed 25-Foot Walk; SSST: Six Spot Step Test; 2MWT: 2-min Walk Test; MSWS-12: 12-Item MS Walking Scale.

the observed lack of fampridine-induced change in gait quality cannot be ascribed to a flooring effect.

A previous study demonstrated a minor fampridine-induced improvement in kinematic knee ROM of 2° during treadmill walking (Zörner et al., 2016). Together with current results of no improvements in GVS and GPS, this finding indicates that the kinematic strategy of patients with MS remains unaltered after a period of fampridine treatment. In contrast, a significant improvement of 10% (corresponding to 1.34° in the GPS) was found in patients with MS following one month of medical treatment for spasticity (nabiximols) (Coghe et al., 2015); the median GPS (12.25°) was considerably poorer than that in the current study (9.39°), so direct comparisons especially of the difference in treatment outcome should be made with caution. Furthermore, no anchor-based MS-specific minimal clinically important change is defined for the GPS, and whether the observed change was clinically relevant, can be questioned. Fampridine-induced changes have been observed in some walking kinetics during treadmill walking, albeit on single patient and not group level, and not versus placebo (Weller et al., 2020). Interestingly, the sub-group of patients displaying kinetic changes, also exhibited improvements in clinical walking tests. Thus, indicating that improvements in gait kinetics potentially influences gait performance, measured by clinical walking tests (Weller et al., 2020).

Compared to controls, patients with MS have demonstrated reduced velocity, cadence, and step length as well as increased base of support (Givon et al., 2009). To the best of our knowledge, only two studies (Allart et al., 2015; Rodriguez-Leal et al., 2018) have examined changes in spatiotemporal parameters in patients with MS following fampridine treatment. Both studies (Allart et al., 2015; Rodriguez-Leal et al., 2018) evaluated the Functional Ambulation Profile (FAP) score, which is composite value of gait based on selected spatiotemporal parameters (Givon et al., 2009). A significant positive change in FAP score was detected in both studies although one based the conclusion on group-level analysis (Rodriguez-Leal et al., 2018) and the other used a categorical responder criterion threshold of 15% (Allart et al., 2015). The latter additionally evaluated the spatiotemporal parameters separately, finding significant improvements in walking speed, cadence, and step-length (Allart et al., 2015). Compared to our study, participants in both studies were more impaired at baseline according to clinical performance tests. Furthermore, unlike our study, the two previous studies did not match walking speed between sessions (Allart et al., 2015; Rodriguez-Leal et al., 2018), potentially introducing a biasing factor on gait variables (including spatiotemporal parameters and joint kinematics).

4.3. Gait performance

In contrast to measures of gait quality, significant improvements were seen on performance-based measures after fampridine treatment with the MSWS-12 showing the largest percentage improvement (−22.5 points/−35.2%). This positive change is substantial compared to most previous studies (Brambilla et al., 2016; Lo et al., 2015; Rodriguez-Leal et al., 2018) and represents an improvement larger than the defined minimal clinically important change from the patient's and therapist's perspectives (10.4 points and 11.4 points, respectively) (Baert et al., 2014).

The 2MWT also showed a large improvement (18.2%). Despite its strong discriminatory ability, the 2MWT has rarely been used to examine the effect of fampridine at group level, but a change of 14.8% was reported in a study on the response to fampridine (Rodriguez-Leal et al., 2018). Although the previous study differed slightly in baseline EDSS characteristics and the participants covered a shorter distance in the 2MWT (Rodriguez-Leal et al., 2018), both that study and our study

obtained the minimally clinical important change value of 9.6 m (patient perspective) and 6.8 m (therapist perspective) (Baert et al., 2014).

The current improvements of −11.5% in T25FW and − 13.9% in SSST are in line with previously reported results in patients with MS (Jensen et al., 2014; Lo et al., 2015). Notably, the group mean change does not reach the defined clinical relevancy of 20% for the T25FW (Hobart et al., 2013), which is often considered the response criterion for continued treatment with fampridine (Hobart et al., 2013; Jensen et al., 2014). Similarly, SSST does not reach the threshold of >19% change for it to be considered a real change exceeding the measurement variability (Callesen et al., 2019). These thresholds however, may have been defined in patients with MS who display a higher level of gait limitations since their basis test results (mean T25FW: 8 to 45 s (Hobart et al., 2013); SSST: 5.6 to 61.1 s (Callesen et al., 2019) are substantially inferior to those demonstrated in our sample (mean T25FW: 6.3 s; mean SSST: 11.9 s). The case-mix of responders and non-responders in the current study may also explain the failure to achieve the thresholds for the T25FW and SSST.

We found no association between improvement in gait quality and improvement in gait function. In view of the large and significant improvements seen in the functional tests and self-perceived gait function, the lack of change in gait quality is not due to a lack of response to fampridine. Instead, the positive fampridine effect on gait function is perhaps a result of improved signal conduction that results in a faster muscular response, rather than a direct effect on the movement pattern and thus kinematic gait quality evaluated by GPS and GVS. Improved gait quality would theoretically include a change in the MS patient's neuromechanical movement strategy, which most likely requires more than the short-term alteration of signal conduction in demyelinated axons that fampridine offers. The current lack of change in gait quality could thus be a consequence of both the short intervention and the isolated biochemical impact of fampridine. Future studies with longer intervention periods, possibly supplemented with targeted gait rehabilitation, are warranted to evaluate the potential influence of fampridine treatment on gait quality in patients with MS.

4.4. Strengths and limitations

Our study provides useful new clinical data on fampridine's effect on kinematic gait quality to add to its known impact on gait function in patients with MS. A further strength is that our GPS calculations were based on data from an able-bodied, age-matched reference group that were collected in our own laboratory. In addition, despite Baker et al. 2009 previously documented a weak correlation between GPS and walking speed (rho = −0.28) (Baker et al., 2009), we chose to match walking speed between sessions to fully eliminate its potential influence on kinematic variables (Filli et al., 2018).

The present study has some methodological limitations. First, the pragmatic clinical approach entailed the inclusion of a sample including both fampridine responders and non-responders. This ruled out a randomized controlled trial approach, and thus also a causal investigation. The non-controlled and un-blinded design raises the possibilities of placebo effect, performance bias, and recall bias, all of which could influence the results. However, fampridine has previously been tested against placebo, and the extensive body of literature supporting a positive fampridine effect on gait function during a two-week trial (Allart et al., 2015; Goodman et al., 2009; Goodman et al., 2010; Lo et al., 2015; Zörner et al., 2016) supports the current results.

Although the sample size was defined a priori, this was based on a minimally clinically important GPS difference derived from children, as a MS-specific anchor-based difference was not available. In addition, the small sample size potentially reduces generalizability to the larger MS population. However, even though only 14, out of the 26 participants who were randomly allocated to 3DGA, accepted to perform this examination, a sub-group analysis of those randomized but not willing to undergo 3DGA yielded no difference in patient characteristics, suggesting high external validity.

5. Conclusions

In this prospective cohort study, improved gait function was observed in patients with MS following fampridine treatment according to performance-based tests and self-perceived gait function. However, no improvement in the kinematic quality of gait was seen. This may indicate that the impact of a two-week fampridine treatment is limited to improved signal conduction that leads to better gait performance.

Author contribution

Conception or design of the work: All.
Coordinating the study: MT, AHL, HHN.
Data collection: MT.
Data-analysis: MT, AHL.
Interpretation of data: MT, AHL, HHN, KLL.
Writing – drafting the work: MT, AHL, HHN, KLL.
Writing – Revision and editing of the work: All.
Final approval of the version to be published: All.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Helle Hvilsted Nielsen reports a relationship with Biogen that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Helle Hvilsted Nielsen reports a relationship with Roche that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Helle Hvilsted Nielsen reports a relationship with Sanofi Genzyme that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Helle Hvilsted Nielsen reports a relationship with Merck & Co Inc. that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Helle Hvilsted Nielsen reports a relationship with Novartis that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Helle Hvilsted Nielsen reports a relationship with Teva Pharmaceutical Industries Ltd. that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Henrik Boye Jensen reports a relationship with Biogen that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Henrik Boye Jensen reports a relationship with Roche that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Henrik Boye Jensen reports a relationship with Sanofi Genzyme that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Henrik Boye Jensen reports a relationship with Merck & Co Inc. that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Henrik Boye Jensen reports a relationship with Novartis that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Henrik Boye Jensen reports a relationship with Teva Pharmaceutical Industries Ltd. that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement.

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