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Clinical study

A cross-sectional comparison of performance, neurophysiological and MRI outcomes of responders and non-responders to fampridine treatment in multiple sclerosis – An explorative study

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ABSTRACT

Objective: To compare baseline physical and cognitive performance, neurophysiological, and magnetic resonance imaging (MRI) outcomes and examine their interrelationship in participants with Multiple Sclerosis (MS), already established as either responder or non-responder to Fampridine treatment, and to examine associations with the expanded disability status scale (EDSS) and 12-item MS walking scale (MSWS-12).

Methods: Baseline data from an explorative longitudinal observational study were analyzed. Participants underwent the Timed 25-Foot Walk Test (T25FW), Six Spot Step Test (SSST), Nine-Hole Peg Test, Five Times Sit-to-Stand Test, Symbol Digit Modalities Test (SDMT), neurophysiological testing, including central motor conduction time (CMCT), peripheral motor conduction time (PMCT), motor evoked potential (MEP) amplitudes and electroneuronography of the lower extremities, and brain MRI (brain volume, number and volume of T2-weighted lesions and lesion load normalized to brain volume).

Results: 41 responders and 8 non-responders were examined. There were no intergroup differences in physical performance, cognitive, neurophysiological, and MRI outcomes (p > 0.05). CMCT was associated with T25FW, SSST, EDSS, and MSWS-12, (p < 0.05). SDMT was associated with the number and volume of T2-weighted lesions, and lesion load normalized to brain volume (p < 0.05).

Conclusion: No differences were identified between responders and non-responders to Fampridine treatment regarding physical and cognitive performance, neurophysiological or MRI outcomes. The results call for cautious interpretation and further large-scale studies are needed to expand our understanding of underlying mechanisms discriminating Fampridine responders and non-responders. CMCT may be used as a marker of disability and walking impairment, while SDMT was associated with white matter lesions estimated by MRI.

ClinicalTrials.gov identifier: NCT03401307.

1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by demyelination in the brain and spinal cord.[1] MS is the most common neuroinflammatory disorder and the leading cause of non-traumatic disability in young adults.[2] Symptoms are protean and consist of palsy, paresthesia, spasticity, diplopia, ataxia, dysphagia, cognitive dysfunction, and sphincter symptoms among others.[1]

Demyelination impairs neural conduction by debilitating ion channel function, which contributes to neuroaxonal injury, neu-

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rodegeneration, and neurological disability.[3] The process of demyelination also exposes potassium channels causing leakage of potassium ions which inhibits nerve conduction.[4]

Fampridine is an inhibitor of primarily voltage-gated potassium channels in demyelinated axons, preventing efflux of potassium ions. This increases action potential amplitude and duration which improves nerve conduction and neurotransmitter release.[5]

Fampridine acts in both the central and peripheral nervous system (PNS).[6] It is the only approved medical treatment for improving walking disabilities in MS, which affects up to 75% of patients[7] and is considered one of the most disabling bodily problems by both MS patients and clinicians.[8] Additionally, Fampridine has beneficial effects on upper extremity function, cognitive performance and quality of life in persons with MS (PwMS). [9–10] Two randomized, double-blind, placebo-controlled trials by Goodman et al. have shown that 35% – 43% of PwMS are responders to Fampridine treatment.[11] A recent study suggests that in PwMS, a normal pre-therapy central motor conduction time (CMCT) may be useful when identifying non-responders to Fampridine treatment.[12] Nonetheless, there are currently no established predictors of Fampridine responsiveness in PwMS.[7]

Magnetic resonance imaging (MRI) of the CNS is widely applied in monitoring disease progression of MS[13] despite its often poor correlation with clinical disabilities in PwMS.[14] However, MRI estimates of brain volume, grey matter volume, white matter diffusion, and T2-weighted lesion volumes are over time correlated with clinical disabilities in PwMS.[15]

When corticospinal tracts are affected by MS lesions, motor evoked potentials (MEPs) are highly capable of detecting and monitoring clinical and subclinical motor nerve conduction alterations, [16] especially in lower extremities.[17] Multimodal evoked potentials can predict future advancement of neurological disabilities in PwMS.[17] However, the current knowledge about the use of MEP in determining MS disease course is limited.[16,18] Furthermore, electroneurographic (ENG) studies of the PNS in PwMS are few, variable in methodology, and inconclusive.[16,19]

Taken together, no studies could be located examining PNS involvement in walking impaired PwMS and its relationship with Fampridine responsiveness, clinical disability measures, nerve conduction in central corticospinal pathways, and MRI outcomes, which was therefore the purpose of the present study.

The main objectives of this study were to identify baseline characteristics of already established responders and non-responders to Fampridine treatment and to examine the interrelationship between physical and cognitive performance, central and peripheral motor nerve conduction, and MRI outcomes in the total study population. Specifically, we aimed at examining Fampridine responders and non-responders regarding:

- Walking performance in terms of the Timed 25-Foot Walk Test (T25FW),[20] and the Six Spot Step Test (SSST),[21] while a proxy for lower body muscle strength was evaluated in terms of the Five Times Sit-to-stand Test (5-STS).[22] Also, manual dexterity was evaluated by the Nine-Hole Peg Test (9-HPT), [23] and cognitive processing speed was evaluated by the Symbol Digit Modalities Test (SDMT). [24]
- Neurophysiological assessment in terms of transcranial magnetic stimulation (TMS) elicited MEPs providing CMCT, peripheral motor conduction time (PMCT), and their respective amplitudes. Furthermore, ENG of the tibial and peroneal nerves examining distal latency, amplitude, nerve conduction velocity (CV), and F-waves.
- MRI of the cerebrum examining brain volume, number of T2-weighted lesions, volume of T2-weighted lesions (lesion load), and lesion load normalized to brain volume.

Furthermore, it was examined in the total study population if:

- The abovementioned outcomes were associated with the degree of neurological disability in terms of the expanded disability status scale (EDSS) and self-reported walking impairment in terms of the 12-Item MS Walking Scale (MSWS-12).
- An Interrelationship between physical and cognitive performance tests, TMS-elicited MEP, ENG, and MRI outcomes exists.

2. Materials and Methods

This paper presents cross-sectional baseline data from an explorative longitudinal observational study investigating a cohort consisting of PwMS who are already defined as being either responders or non-responders to Fampridine treatment (Fig. 1). The two groups are examined and compared regarding physical and cognitive performance tests, TMS-elicited MEPs, ENG of the tibial and peroneal nerves, and MRI parameters of the brain. Responders are defined as PwMS who improve by $\geq$ 20% on the T25FW when receiving 10 mg Fampridine twice daily in a two-week trial. Those whose improvements are below 20% are classified as non-responders.[25]

2.1. Subjects

2.1.1. Recruitment

Eligible participants, who already were established as being responders or non-responders to Fampridine treatment, from the Region of Southern Denmark, were identified and included from the outpatient MS-clinics of the Region of Southern Denmark (Odense, Kolding, Esbjerg, and Sønderborg) and via an announcement from the Danish Multiple Sclerosis Society (Fig. 1).

Sample size calculation for this study estimated that 82 PwMS from whom 29 were responders (35%) and 53 non-responders (65%) to Fampridine treatment (based on response distribution estimated by Goodman et al.)[26] were needed to obtain a statistical power of 80% to detect standardized mean differences of at least 0.68 s on T25FW. For the power calculation, significance level was set at $p \leq 0.05$.

2.1.2. Inclusion and exclusion criteria

To be included, responders and non-responders to Fampridine treatment should be diagnosed with MS in accordance to the McDonald criteria,[27] have an EDSS score below 7, and be in the age group 18–65 years.

Exclusion criteria consisted of risk factors related to peripheral neuropathy (e.g. diabetes mellitus, impaired glucose tolerance, alcohol abuse, radiation treatment, and nutritional disorders), epilepsy, intracranial metal-clips, pacemaker and implanted electronic devices, pregnancy and metallic foreign objects in the eye.

2.2. Standard protocol approvals

The project was approved by the National Committee on Health Research Ethics (project ID: S-20160204) and the Danish Data Protection Agency (journal number: 16/42475). The study was conducted in accordance to the Helsinki Declaration. Clinicaltrials.gov identifier for this study is NCT03401307.

2.3. Examinations

2.3.1. Neurophysiological examinations

Recording of EMG responses of MEP and ENG were conducted using Dantec Keypoint. Single-pulse TMS were performed using a Dantec Magnetic Primer TwinTop & MagLite r-25 Magnet Stimula-
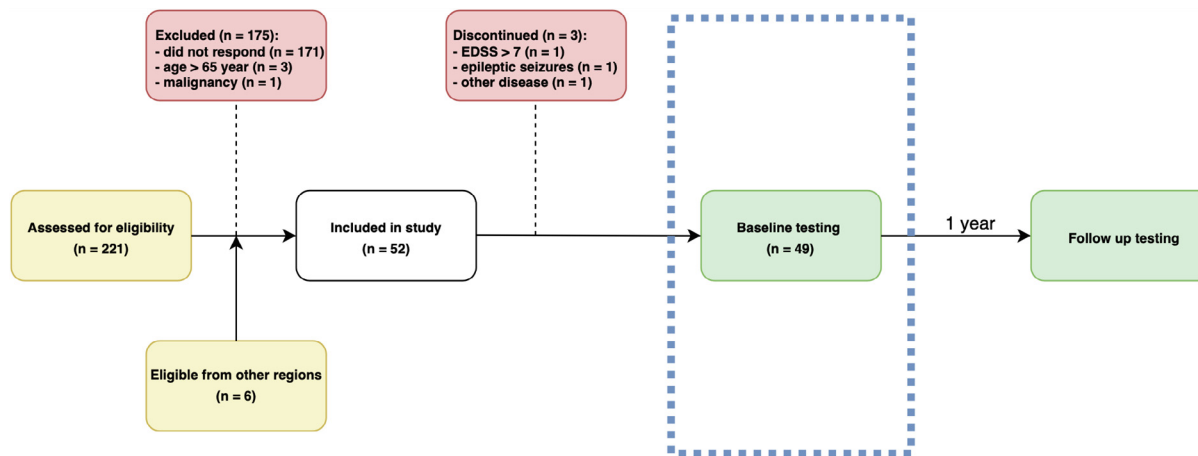
Fig. 1. *Flowchart of study design and participant selection.* The results presented in this paper are from baseline tests (dotted box).

tor and a MagVenture MagPro R30 Transcranial Magnetic Stimulator. A handheld circular coil placed over the vertex was used to stimulate the primary motor cortex (M1). After determination of the resting motor threshold, stimulation intensities of 120% above the threshold were applied. ENG was conducted using a bipolar surface electrode with pulse duration set at 0.1 ms.

In addition to the analysis of individual CMCT, PMCT, and ENG outcomes of each leg (Table 3), the mean of both legs was included for analyses reflecting a global measure of corticospinal involvement in MS, as suggested by Brambilla et al. and Zeller et al. in TMS-elicited MEP-studies.[12,28] This approach is also supported by high asymmetry indices in corticospinal tracts in PwMS, in regards to anatomy and neurophysiological deficits.[29]

2.3.1. MRI acquisition and processing

As the study was multicenter, acquisition of baseline-MRIs of the cerebrum and MS protocols of MRI varied (Table 1).

MRI images were initially denoised[30] corrected for bias field-induced intensity inhomogeneity,[31] registered to the Montreal Neurological Institute (MNI) space[32] and intensity normalized to the ICBM152 template (using respectively T1 and T2 templates). [33] The processed images were then skull stripped using Brain Extraction based on nonlocal Segmentation Technique (BEaST).[34] T2 hyperintense lesions were segmented (Fig. 2) using the Lesion Prediction Algorithm (LPA)[35] as implemented in the Lesion Segmentation Toolbox version 2.0.15 (www.statistical-modelling.de/lst.html) for SPM12 in MATLAB R2016b (MathWorks, Natick, MA).

Whole brain volumes were estimated using skull stripped T2-FLAIR images. T1-weighted images were used for whole brain estimation in cases where these had higher resolutions than T2-FLAIR (n = 5).

2.4. Statistical methods

Data were tested for normality using histograms, QQ plots, and Shapiro-Wilk tests. To evaluate baseline characteristics, descriptive statistics were applied. Normally distributed variables of respon-
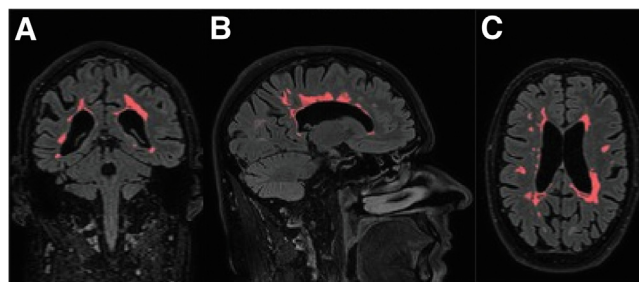

Fig. 2. Magnetic Resonance Imaging (MRI) T2-weighted hyperintense lesion segmentation of persons with Multiple Sclerosis. (A) coronal-, (B) sagittal- and (C) axial planes.

ders and non-responders to Fampridine treatment were compared using unpaired t-tests. Mann-Whitney U tests were utilized in non-parametric tests. Levene's test was applied to assess equal variance assumption and Welch test was applied when variances were unequal. Post hoc comparisons for multiple testing were performed using Bonferroni corrections.

Multilevel mixed effects generalized linear models (MEGLM) were performed to test if examinations of the total study population were associated with EDSS and MSWS-12. Regression models were performed adjusted and unadjusted for interrelationship between EDSS, MSWS-12, physical and cognitive performance tests, neurophysiological, and MRI outcomes.

STATA 15.1 software was utilized for statistical analysis of data. P-values below 0.05 indicated statistical significance.

3. Results

3.1. Baseline demographics

Overall, 221 eligible PwMS, who were responders and non-responders to Fampridine treatment, were identified and invited

Table 1
Magnetic Resonance Imaging (MRI) and voxel sizes utilized in the Region of Southern Denmark.

Site	Vendor	Field strength (T)	T2-FLAIR, voxel size (mm³)	T1, voxel size (mm³)	N
Odense	Siemens	1.5	1.0x1.0x1.0	1.0x1.0x1.0	2
Kolding	Philips	1.5	0.5x0.5x1.0	NA	38
Esbjerg	Siemens	1.5	0.5x0.5x2.5	0.7x0.7x6.5	3
Sønderborg/Aabenraa	Siemens	1.5	0.7x0.7x6.5	0.9x0.9x1.0	5
Kolding	Siemens	3.0	0.5x0.5x1.0	NA	2

Abbreviations: T: Tesla.

from the MS-clinics of the Region of Southern Denmark (Fig. 1). In total, 52 participants were included, of which, 3 participants did not complete the study due to adverse events before baseline testing. Data from 49 participants, were analyzed with 41 responders and 8 non-responders to Fampridine treatment (unmatched).

There were no statistically significant differences (Table 2) between the two groups for any baseline characteristics (p > 0.05). Responders consisted of 22 PwMS with relapse-remitting MS (RRMS) and 19 with progressive MS (PMS) and non-responders consisted of 5 with RRMS and 3 with PPMS.

3.2. Physical and cognitive performance tests

There were no significant differences (Table 2) between groups in physical and cognitive performance tests (p > 0.05).

3.3. Mep and ENG

CMCT was prolonged in both responders and non-responders compared with normal values based on the Danish normal population (Table 3). There was no intergroup difference in CMCT (p > 0.05). PMCT was within normal values in the responders and prolonged in non-responders compared to normal values. There were no intergroup differences in PMCT and MEP amplitudes (p > 0.05).

Four responders were not able to undergo ENG of the right peroneal nerve due to right atrophied extensor digitorum brevis muscle. This also applied to one non-responder for the left peroneal nerve. Intergroup differences (Table 3) were found for the CV of the right tibial nerve without intergroup differences regarding the right leg or mean of both legs. Amplitude of left peroneal nerve also showed significant intergroup difference (p < 0.05), where the mean of both tibial nerve amplitudes was decreased in the non-responders (p = 0.046). There were no differences when comparing latencies and F-waves (p > 0.05). All ENG results were within normal values.[36]

3.4. MRI of cerebrum

Brain volume, number of T2-weighted lesions, volume of T2-weighted lesions (lesion load) and lesion load normalized to brain volume did not yield significant differences (Table 4) between responders and non-responders (p > 0.05).

Table 2
Baseline demographics and physical and cognitive performance tests of responders and non-responders.

	Responders (n = 41)	Non-responders (n = 8)	p-value
Demographics			
Age; years	51.5 ± 8.2	50.1 ± 5.7	0.783[a]
Disease duration;	16.0 ± 7.0	18.5 ± 8.2	0.216[b]
years	5.0 ± 1.3	4.6 ± 1.3	0.318[b]
EDSS; a.u.	43.1 ± 10.4	44.0 ± 11.8	0.497[a]
MSWS-12; a.u.	8.5 ± 9.5	8.6 ± 6.0	0.665[b]
Performance			
T25FW; sec			
SSST; sec.	14.5 ± 20.3	14.3 ± 8.9	0.892[b]
5-STS; sec	11.9 ± 5.8	14.1 ± 5.3	0.457[b]
9-HPT; sec.	27.5 ± 12.4	33.3 ± 9.8	0.150[c]
SDMT; a.u.	40.2 ± 10.6	39.8 ± 5.8	0.920[a]

Note. Mean values ± standard deviation. Bold p-values indicate statistical significance (p < 0.05), [a]: p-values were derived from unpaired t-tests, [b]: Mann-Whitney *U* test, and, [c]: p-value derived after Bonferroni correction for multiple testing. *Abbreviations*: a.u.: arbitrary units, EDSS: Expanded Disability Status Scale, MSWS-12: 12-Item MS Walking Scale, a.u.: arbitrary units, T25FW: Timed 25-Foot Walk Test, SSST: Six Spot Step Test, 5-STS: Five Times Sit-to-Stand Test, 9-HPT: Nine Hole Peg Test, and SDMT: Symbol Digit Modalities Test.

3.5. Physical and cognitive performance tests, neurophysiological examinations, and MRI and associations with disability

In MEGLM of the total study population of PwMS, the T25FW was the only performance test associated with the EDSS (p = 0.022). The MSWS-12 demonstrated no associations with physical and cognitive performance tests (p > 0.05).

Furthermore, EDSS and CMCT of the left motor pathways were associated (p < 0.01) in the total study population, unlike the CMCT of the right motor pathways (p = 0.098). Mean CMCT was associated with EDSS (p = 0.026). Both CMCT of the left and right motor pathways and their average were also associated with MSWS-12 (p < 0.01) while PMCTs were not associated with EDSS or MSWS-12 (p > 0.05).

None of the fully and partly adjusted and univariate analyses of ENG outcomes in the total study population of PwMS showed any associations with EDSS and MSWS-12 (p > 0.05). Likewise, MRI brain outcomes were not associated with EDSS or MSWS-12 (p > 0.05).

3.6. Central motor conduction times and physical and cognitive performance tests

MEGLM of CMCT in the total study population showed that CMCT of the left motor pathways was associated with T25FW (p = 0.021) unlike the CMCT of the right motor pathways (p = 0.071). Mean CMCT was associated with the T25FW (p = 0.028). All CMCT aspects were associated with SSST (p < 0.01) and 9-HPT (p < 0.021), whereas CMCT was not associated with 5-STS and SDMT (p > 0.05).

3.7. Physical and cognitive performance tests, neurophysiological outcomes and associations with MRI outcomes

MEGLM of the total study population of PwMS did not identify any associations between any MRI outcomes and T25FW, SSST, 5-STS, 9-HPT, CMCT, and ENG outcomes (p > 0.05). Linear regression analysis showed that SDMT was not associated with brain volume (p = 0.653, R^2= 0.004), while being associated with the number of T2-weighted lesions (p = 0.011, R^2= 0.122). MEGLM analysis showed that SDMT was associated with the volume of T2-weighted lesions (lesion load) and lesion load normalized to brain volume (p < 0.05). Furthermore, linear regression analysis demonstrated association between high age and lower score on the SDMT (p < 0.001, R^2= 0.202).

4. Discussion

The present explorative study identified no differences between already established Fampridine responders and non-responders regarding age, disease duration, EDSS, MSWS-12, physical and cognitive performance tests, and MRI outcomes. No clear intergroup differences regarding neurophysiological examinations were observed. CMCT of the total study population was associated with both EDSS and MSWS-12, except for ENG and MRI outcomes. SDMT of the total study population was strongly associated with the number of T2-weighted lesions and their volumes (lesions load) and lesion load normalized to brain volume.

4.1. PMCT and peripheral nerve affection in MS

PMCT values were prolonged only in non-responders to Fampridine treatment compared to normal values. The PMCT represents conduction times in the proximal part of the PNS[37] and may suggest slowing of nerve conduction in the proximal part of

Table 3
Motor evoked potentials and electroneuronographic examinations of the tibial and peroneal nerves in responders and non-responders to Fampridine treatment.

	Normal values	Responders (n = 41)			Non-responders (n = 8)			p-values		
		Right	Left	Mean of both sides	Right	Left	Mean of both sides	Right-right	Left-left	Mean of both sides
CMCT; ms	13.7 – 18.1	24.2 ± 9.2	22.2 ± 6.2	23.2 ± 7	28.2 ± 10.7	24.1 ± 9.4	26.1 ± 9.9	0.448[b]	0.604[b]	0.498[b]
PMCT VM muscle; ms	8.7 – 9.9	9.7 ± 1.3	9.6 ± 1.2	9.6 ± 1.1	11.0 ± 3.3	11.5 ± 4.2	11.2 ± 3.6	0.288[c]	0.245[c]	0.245[c]
PMCT TA muscle; ms	13.9 – 15.5	15.3 ± 1.8	15.0 ± 1.4	15.2 ± 1.4	16.0 ± 2.7	19.9 ± 10.0	18.0 ± 6.0	0.339[a]	0.213[c]	0.228[c]
MEP amplitude cortex to VM muscle; mV	NA	0.9 ± 0.8	0.8 ± 0.8	0.9 ± 0.7	0.8 ± 0.5	0.9 ± 1.0	0.9 ± 0.7	0.818[b]	1.000[b]	0.73 5[b]
MEP amplitude spine to VM muscle; mV	NA	1.8 ± 2.3	1.8 ± 1.9	1.8 ± 1.8	0.8 ± 0.8	0.9 ± 0.5	0.8 ± 0.6	0.070[b]	0.204[b]	0.083[b]
MEP amplitude cortex to TA muscle; mV	NA	1.6 ± 1.6	1.6 ± 1.4	1.6 ± 1.4	1.2 ± 1.1	0.9 ± 0.5	1.0 ± 0.7	0.685[b]	**0.010[c]**	0.082[c]
MEP amplitude spine to TA muscle; mV	NA	0.8 ± 1.0	0.8 ± 0.7	0.8 ± 0.5	0.8 ± 0.7	0.8 ± 0.4	0.8 ± 0.6	0.829[b]	0.646[b]	0.978[b]
Latency peroneal nerve; ms	3.1 – 6.9	4.6 ± 0.8*	4.5 ± 0.8	4.5 ± 0.7	4.9 ± 1.1	4.4 ± 0.5**	4.6 ± 0.7	0.255[a]	0.754[a]	0.787[a]
Amplitude peroneal nerve; mV	0.4 – 11.7	6.6 ± 3.2*	6.3 ± 2.8	6.4 ± 2.6	4.2 ± 1.7	6.2 ± 3.2**	5.2 ± 1.0	**0.006[c]**	0.968[a]	**0.046[c]**
CV peroneal nerve; m/s	42 – 56	45.6 ± 5.8*	46.7 ± 6.5	46.2 ± 5.8	44.0 ± 5.6	45.2 ± 7.4**	44.7 ± 6.3	0.480[a]	0.640[b]	0.622[b]
F-wave peroneal nerve; ms	45.1 – 67	52.6 ± 5.4*	53.3 ± 5.7	53.0 ± 5.3	54.4 ± 7.5	54.4 ± 4.5**	54.4 ± 5.7	0.424[a]	0.608[a]	0.526[a]
Latency tibial nerve; ms	3.2 – 7.4	4.1 ± 0.6	3.9 ± 0.7	4.0 ± 0.6	3.8 ± 0.8	3.6 ± 0.8	3.7 ± 0.7	0.285[a]	0.229[b]	0.245[a]
Amplitude tibial nerve; mV	1.8 – 25.6	15.2 ± 7.5	14.8 ± 7.8	15.0 ± 6.7	12.2 ± 10.7	15.5 ± 10.0	13.8 ± 10.2	0.343[a]	0.817[a]	0.695[a]
CV tibial nerve; m/s	42 – 56	43.9 ± 6.3	42.2 ± 5.5	43.1 ± 5.0	39.0 ± 5.7	40.6 ± 3.9	39.8 ± 3.7	**0.044[a]**	0.440[a]	0.083[a]
F-wave tibial nerve; ms	45.1 – 67.0	53.5 ± 4.5	53.2 ± 5.6	53.3 ± 4.8	55.0 ± 7.5	56.0 ± 4.4	55.5 ± 5.1	0.477[a]	0.189[a]	0.244[a]

Note. Mean values ± standard deviation. Bold p-values indicate statistical significance. [a]: p-values were derived from unpaired t-tests and, [b]: Mann–Whitney *U* test, [c]: p-values derived by Welch test, [d]: p-value derived after Bonferroni correction for multiple testing, *: in responders n = 37 and **non-responders n = 7. *Abbreviations*: VM: Vastus medialis, TA: Tibialis anterior, CV: conduction velocity, CMCT: central motor conduction time and PMCT: peripheral motor conduction time. MEP *normal values* are based on Danish normal population and ENG reference values from Buschbacher et al. 2000.[36].

Table 4
Magnetic resonance imaging of the cerebrum of responders and non-responders to Fampridine treatment.

MRI outcome	Responders (n = 41)	Non-responders (n = 8)	p-value
Brain volume; ml	1377 ± 147	1474 ± 131	0.092[a]
Number of T2-weighted lesions	19.2 ± 10.0	18.1 ± 6.4	0.735[b]
Volume of T2-weighted lesions (lesion load); ml	8.9 ± 12.6	10.3 ± 9.5	0.208[b]
Lesion load normalised to brain volume; ‰	14.0 ± 7.1	12.3 ± 4.4	0.527[a]

Note: Mean values ± standard deviation). [a]: p-values were derived from unpaired t-tests and [b]: Mann-Whitney *U* test.

lower extremities in non-responders. It should be noted that the evaluation of PMCT presents challenges, as it is challenging to elicit supra-maximal compound muscle action potentials (CMAP).[37]

The impact of MS in the lower extremities has been reported by Jende et al.,[19] who demonstrated a higher number of T2-weighted hyperintense magnetic resonance neurography imaging lesions in the sciatic nerve alongside higher tibial and peroneal nerve calibres in PwMS compared to healthy controls.[19] Simultaneously, the same study found normal motor ENG outcomes of tibial and peroneal nerves.[19] It has been hypothesized that demyelinating peripheral neuropathy in MS could be derived from epitope spreading as a part of the MS disease mechanism.[38] Axonal and Wallerian degeneration are significant components of neurodegeneration and contribute to disease progression in MS.[39] However, Jende et al. ruled out the possibility of Wallerian degeneration in the PNS in PwMS due to diffuse and non-focal lesion distribution of lesions suggesting underlying inflammatory or demyelinating mechanisms, whereas Wallerian degeneration usually involves longer fascicular segments or somatotopic organization.[19,40]

Our findings are challenged by the low number of non-responders. However, if the trend of prolongated PMCT in non-responders could be verified in larger studies, it may suggest extension of MS into the PNS. Fampridine also has shown to be myelo- and axonoprotective,[41–42] which may perhaps, on a long-term basis, delay neuronal compensatory overexpression of sodium channels causing neuroaxonal damage.[3] The possibility of PMCT-prolongation may indicate (1) extension of MS disease mechanisms to the PNS in non-responders who do not receive Fampridine or (2) may indicate a neuroprotective effect on the PNS of the responder group, while it also can be a combination thereof.

Involvement of the PNS is of interest in PwMS or among non-responders to Fampridine treatment displaying discrepancies regarding low CNS disease activity and a high degree of clinical disability. It has also been suggested that walking disabilities in non-responders to Fampridine treatment with prolonged CMCT may be caused by axonal loss or factors outside the corticospinal tract.[12]

4.2. Central motor conduction times and disability

CMCT was associated with disability, in terms of EDSS and MSWS-12 (p < 0.05). Accordingly, CMCT has previously demonstrated to be a predictor of EDSS.[43] The small difference between right and left CMCTs in this study is likely explained by the asymmetric effect of MS lesions in the corticospinal pathways.[29] Importantly, MEPs are highly capable of detecting alterations in nerve conduction in corticospinal tracts affected by MS lesions, and can help identify PwMS at high risk of disease progression.[44]

4.3. Fampridine responsiveness, MRI, and the clinico-radiological paradox

Brambilla et al. compared diffusion tensor imaging (DTI) in PwMS before and after treatment with Fampridine, where responders to Fampridine treatment had a significant reduction in mean diffusivity

(MD) and radial diffusivity (RD) in the corticospinal tracts compared to non-responders.[28] These changes in the responders were assumed caused by Fampridine-induced closure of potassium channels modifying the osmotic balance of water molecules across axonal membranes causing changes in corticospinal tract MD and RD. Compared to conventional MRI, DTI demonstrated higher sensitivity in highlighting axonal damage and corticospinal tract MD are stronger associated with walking impairments in MS.[45] DTI and brain corticospinal MD has been suggested as a biomarker predicting Fampridine responsiveness.[45]

None of the MRI outcomes in the study population were associated with physical performance, EDSS, or MSWS-12, supporting the term "clinico-radiological paradox", where MRI lesions are poorly associated with disabilities in MS.[14] In this study, SDMT was associated with number and volume of T2-weighted lesions, and lesion load normalized to brain volume. Adding support to this finding, information processing speed in PwMS has been shown to be impaired by white matter damage, MRI lesion load,[46] and brain volume changes.[47] Due to its stronger correlation with MRI parameters, SDMT has been suggested to replace the Paced Auditory Serial Addition Test in the Multiple Sclerosis Functional Composite.[47]

5. Clinical implications

Results demonstrate that CMCT is a useful marker of clinical disability in PwMS. Furthermore, our results suggest that deteriorating SDMT performance shall prompt referral to an MRI of the cerebrum. This study further suggests that implementation of CMCT and SDMT as routine examinations in MS could be useful in monitoring disease progression and potentially identifying PwMS, who are at higher risk of disease progression.

6. Limitations

This study was limited by the small number of non-responders compared to responders to Fampridine treatment (16.3% vs. 83.7%). Recent studies have estimated a higher proportion of responders to Fampridine treatment at 50.9% and 70%.[10,48] It is suggested that, in a real-world clinical setting, a higher proportion of PwMS demonstrates beneficial effects of Fampridine than suggested in previous clinical trials by Goodman et al..[11,49] Furthermore, studies examining Fampridine responsiveness are mainly focused on walking impairments, while it has been demonstrated that Fampridine also improves cognition, dexterity,[9–10,50] fatigue and quality of life.[10]

The small size of non-responders caused the study to be underpowered, which increased risk of type II errors and added to a relatively high standard deviation.

Examined participants were already established as responders or non-responders to Fampridine treatment. Results may have differed if PwMS eligible for Fampridine treatment were examined before initiating treatment, as CMCT is known to be reduced after treatment with Fampridine.[28]

Being a multicentre study resulted in the utilization of different MRI scanners and scanning sequences, which can have different sensitivities regarding detection of T2-weighted lesions.

The study population did not undergo MRI of the spinal cord, where lesions can contribute to the disease course. Furthermore, MEP was not conducted in upper extremities.

7. Conclusion

There were no intergroup differences regarding physical and cognitive performance, neurophysiological, or MRI outcomes between responders and non-responders to Fampridine treatment. CMCT was associated with the disability measures EDSS and MSWS-12 and performance tests T25FW, SSST, and 9-HPT. Furthermore, SDMT was strongly associated with the number- and volume of T2-weighted lesions (lesion load) and lesion load normalized to brain volume on MRI of the cerebrum.

Our results call for cautious interpretation due to a low number of non-responders. A well-powered study comparing responders and non-responders to Fampridine treatment is warranted. Furthermore, longitudinal studies applying the same outcome measures are warranted, where PwMS are examined before establishing their Fampridine responsiveness status.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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