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Motoric cognitive risk syndrome in people with multiple sclerosis: prevalence and correlations with disease-related factors

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Abstract

Background: The motoric cognitive risk (MCR) syndrome, defined as the coexistence of slow gait and subjective cognitive complaints, has as yet not been researched in people with multiple sclerosis (pwMS).

Objective: To examine the prevalence of the MCR syndrome in pwMS and its association with disability, disease duration, perceived fatigue, and fear of falling.

Methods: The study comprised 618 pwMS [43.7 (SD = 12.6) years, 61.7% females]. Gait speed was measured by the GAITRite™ electronic walkway (CIR Systems, Inc. Haverton, PA, USA). Cognitive status was defined according to the global cognitive score computed by the NeuroTrax™ cognitive battery (NeuroTrax Corporation, Medina, NY, USA). The sample was divided into four main groups: 'normal', 'cognitively impaired', 'gait impaired' or 'MCR'. Perceived fatigue was assessed by the Modified Fatigue Impact Scale; fear of falling by the Falls Efficacy Scale International.

Results: Sixty-three (10.2%) patients were diagnosed with MCR. The percentage of subjects categorized as MCR was 26.0% in severely disabled pwMS compared with 10.9%, 6.0%, and 4.6% in moderately, mildly and very mildly disabled pwMS, respectively. Subjects in the MCR group presented with elevated fatigue compared with patients classified as normal [49.7 (SD = 23.3) vs 26.5 (SD = 19.2), $p < 0.001$]. Fear of falling was significantly higher in the MCR and gait impairment groups compared with the cognitively impaired and normal groups.

Conclusions: The current study corroborates the presence of MCR in pwMS. Nevertheless, future longitudinal research is warranted to better understand its application.

Keywords: cognition, fatigue, gait, MCR syndrome, multiple sclerosis

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Introduction

The Motoric Cognitive Risk (MCR) syndrome was first proposed by Verghese *et al.*[1] in 2013 as a functional marker aimed at identifying older individuals at a high risk for transitioning to dementia. Verghese *et al.* and Ayers *et al.*, defined MCR as the coexistence of slow gait and subjective cognitive complaints in the absence of dementia and significant mobility disability.[1,2] Previous studies have shown that MCR is associated with an increased risk of dementia,[1,3,4] disabilities,[3] falls,[5] and mortality.[6] Recently, Bortone *et al.*[7] reported that elders who were diagnosed with MCR were less educated, more depressed, exhibited more exhaustion, suffered from lower muscle strength, performed less physical activity, and presented with increased levels of systemic inflammation compared with age and sex-adjusted controls.

The MCR syndrome might be relevant for people with multiple sclerosis (pwMS). Multiple sclerosis (MS), the most common chronic immune-mediated disorder affecting the central nervous system, is characterized by gait and cognitive

impairments that are prevalent and debilitating.[8] Impaired gait (>80%) is a common and often an early symptom of MS.[9,10] MS-related gait difficulties contribute to a high risk of falling, as well as a reduced quality of life (QoL) and other negative real-world outcomes.[11,12] Similarly, cognitive impairment occurring in ~50% of pwMS[13] has been found associated with a host of negative consequences including depression, isolation, and a reduced QoL.[14–16] Importantly, gait and cognitive impairments tend to co-occur in pwMS (i.e. cognitive-motor coupling).[17,18] These co-occurrings and interrelated MS manifestations may be due to shared neural mechanisms that underlie both domains of functioning.[19]

According to our literature search, MCR has as yet not been studied in pwMS. There is scarce data as to the possibility of MCR in people with central nervous system (CNS) damage or diseases. Verghese *et al.*[20] found that stroke (HR: 1.42, 95%CI: 1.14–1.77), and Parkinson's disease (HR: 2.52, 95% CI: 1.68–3.76) predicted a higher risk of incidence of MCR after age, sex and education adjustment. Several reasons justify the rationale for screening pwMS for MCR. First, this index might help in determining an MS diagnosis by specifically accelerating detection of a transition from the relapsing-remitting to the secondary progressive form of the disease. This issue is particularly important, given that there is no clear-cut boundary between these two forms of MS. A period of diagnostic uncertainty has been reported to last almost 3 years.[21] Moreover, indicators of secondary-progressive MS may be subtle, and invisible to the naked-eye. Second, this index may be more advantageous, vis-a-vis the standard clinical measures in revealing functionality. Significantly, the MCR syndrome has not been described as a replacement of the well-documented clinical measures used in the MS population (i.e. EDSS, functional systems score, MSQOL inventory, etc.). Furthermore, we are aware that MCR criteria do not take into account significant symptoms of MS such as fatigue and upper limb function. Nevertheless, due to its simplicity, feasibility and relevancy for pwMS, the MCR syndrome is worth investigating. Moreover, MCR might be preferred over common clinical measures as an early marker of MS disease progression, thus, enabling timely implementation of preventive strategies. Therefore, the primary aim of this study was to examine the prevalence of the MCR syndrome in pwMS and its association with disability (i.e. EDSS), disease duration, perceived fatigue, and fear of falling. Furthermore, we expanded the definition of the standard MCR syndrome by classifying subgroups based on combinations of slow/very slow walking speed and moderate/severe cognitive decline.

Materials and methods

Study design and participants

Our cross-sectional study comprised 618 pwMS [43.7 (SD = 12.6) years, 61.7% females] recruited from the Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, Israel from 1/2012-9/2021. Data were extracted from the center's computerized database, a population-based registry documenting demographic, clinical and imaging data of all consecutive PwMS followed at the center. The integrity of the data registry was evaluated by a computerized logic-algorithm-questioning process identifying data entry errors. A computerized questionnaire was employed to assist in choosing PwMS according to the following inclusion criteria: (1) a neurologist-confirmed diagnosis of definite MS according to the revised McDonald criteria;[22] (2) Expanded Disability Status Scale (EDSS) $\leqslant$ 6.5, equivalent to walking ~20 m with bilateral support;[23] (3) treatment with disease modifying drugs for at least 6 months; (4) completion of a instrumented gait assessment via an electronic walkway; (5) completion of a computerized cognitive battery of tests; (6) completion of patient report outcome measures indicating a level of perceived fatigue and fear of falling; and (7) cognition, perceived fatigue, fear of falling and gait assessment assessed within a 6-month period. Exclusion criteria included (1) corticosteroid treatment within 60 days prior to assessment or within the 6-month period in-between assessments, (2) ingesting medications such as fampridine that could interfere with walking, (3) other significant neurological or psychiatric illnesses, (4) alcohol or drug abuse, (5) orthopedic disorders that could negatively affect walking, and (6) participation in a motor and/or cognitive rehabilitation study during the testing sessions.

Each patient's record was referenced by an anonymous code number to ensure confidentiality during the statistical analyses. Hence, individual data will not be made available in order to protect the participants' identity.

Motoric cognitive risk (MCR)

The MCR syndrome was first defined by Verghese *et al.*[1] In general, pwMS manifesting a slow gait and impaired cognition were classified as MCR. Although, the original definition of MCR did not require complex cognitive testing, we defined the subject's cognitive status according to the scores derived from a computerized cognitive testing battery tool. Gait speed was measured by walking on a computerized walkway, exactly as performed in Verghese *et al*'.s original study.[1] Measures of walking speed and cognitive performance are detailed as follows:

Walking speed. Gait speed was measured by the GAITRite™ 4.6-meter electronic walkway (CIR Systems, Inc. Haverton, PA, USA), a valid tool for measuring spatio-temporal parameters of gait in various populations, including pwMS,[24] and has been used in numerous research studies and clinical trials. A single valid walking trial was defined once the participant walked independently, at his own self-selected speed, in one direction across the electronic mat without stopping. Each participant performed six consecutive walking trials. Walking speed was individually calculated for each pass. All trial values were then averaged to produce the final result. Walking speed was classified into 3 subcategories: (1) 'normal'; (2) 'slow' (gait speed between 1 to 2 SD below age- and gender mean values);[25] and (3) 'very slow' (gait speed 2 SD below the normative walking speed reference). pwMS who were classified as slow and or very slow, met the walking speed criteria for MCR.

Cognition. Cognitive performance was assessed by a battery of computerized tests (NeuroTrax Corporation, Medina, NY, USA). The NeuroTrax cognitive battery test has been authenticated in pwMS, and has shown good discriminant and construct validity compared to a conventional cognitive assessment.[26,27] The battery is easily administered. Testing included the following cognitive domains: memory (verbal and nonverbal), executive function, attention, information processing speed, visual spatial processing, verbal function and motor skills. Each cognitive score was standardized relative to age-/education. stratified cognitively intact norms and presented in an IQ style scale. Cognitive domain scores were computed as the average scores from particular tests (see[26,28] for more details). A global cognitive score (GCS) was computed as the average of the cognitive domain scores. Testing time was ~45 minutes. The computerized cognitive battery has shown good test–retest reliability and construct validity compared to paper-based tests, including the frequently used Neuropsychological Screening Battery for MS,[26] as well as sensitivity to effects of disease modifying drugs in pwMS.[29] Cognitive performance was categorized according to previous research findings in the MS population,[28] as 'normal' (GCS $\geqslant$ 100), 'moderately impaired' (GCS 85-99) or 'severely impaired' (GCS $<$ 85). pwMS classified as moderately and/or severely impaired, met the cognitive impairment criteria for MCR.

Perceived fatigue

Perceived fatigue was assessed by the Modified Fatigue Impact Scale (MFIS), a multidimensional 21-item questionnaire acquiring information as to the effects of fatigue–physical (9-items), psychosocial (2-items) and cognitive (10-items) domains over a 4-week period. pwMS rated the 21 items using a 5-point Likert-type scale, ranging from never (0) to always (4); the higher the score, the more the perceived fatigue. Advantages of the MFIS include easy use, good reliability over a 6-month period and a strong correlation with the Fatigue Severity Scale results.[30]

Fear of falling

The participant's self-reported questionnaire, the Falls Efficacy Scale International (FES-I), a common measure of fear of falling[31] assessed the level of concern of falling during 16 activities of daily living ranging from basic to more demanding, including social activities that may contribute to the Qol. Level of concern for each item was scored using a four-point scale (1 = not at all concerned, 4 = very concerned) within a total score range of 16–64; the higher the score, the more the fear of falling. van Vleit *et al.*[32] reported that the FES-I is appropriate for research and clinical purposes in pwMS.

Statistical analysis

The sample group was divided into four main groups according to cognitive performance and walking speed: 'normal' or 'cognitively impaired' (with normal walking speed); 'gait impaired' (with normal cognition); or MCR. Subsequently, the 'cognitively impaired' participants were

Table 1. Main group and subgroup categorization.

Main group	Subgroup	Gait speed	Cognition
Normal		Normal	Normal
Cognitively impaired	Moderately impaired	Normal	Moderate
	Severely impaired	Normal	Severe
Gait impaired	Slow speed	Slow	Normal
	Very slow speed	Very slow	Normal
MCR	Slow speed + moderate cognition	Slow	Moderate
	Very slow speed + moderate cognition	Very slow	Moderate
	Slow speed + severe cognition	Slow	Severe
	Very slow speed + severe cognition	Very slow	Severe

MCR, motoric cognitive risk.
Cognition is categorized by the Global Cognitive Score (GCS) as 'normal' (=GCS $\geqslant$ 100), 'moderate' (=GCS 85–99) or 'severe' (=GCS $<$ 85). Gait speed is classified as 'normal'; 'slow' (=gait speed between 1 to 2 SD below age- and gender mean values); and 'very slow' (=2 SD below the normative walking speed reference).

subdivided into 'moderately impaired' and 'severely impaired'; 'gait impaired' were subdivided into 'slow' or 'very slow'. pwMS classified with MCR were subdivided into four subgroups based on combinations of moderately/severely impaired cognition with slow/very slow walking speed. Group categorization of the study sample is presented in Table 1.

Descriptive statistics characterized the participants' demographic and clinical traits. The chi-square test examined the differences between groups and subgroups by gender, and by one-way analysis of variance tests for age, disease duration, mean EDSS, walking speed, global cognitive score, perceived fatigue (MFIS), and fear of falling (FES-I). The extent of disability, determined by the EDSS score, (subdivided into four subgroups) was 'very mild' (EDSS: 0–1.0), 'mildly' (EDSS: 1.5–2.5), 'moderately' (EDSS: 3.0–4.5), and 'severely' (EDSS: 5.0–6.5) disabled. The extent of disease duration (subdivided into five subgroups) was: up to 1 year, between 1 to 5, 6 to 10, 11 to 20, and $>$ 20 years.

A series of proportion *Z*-tests were performed to determine the differences between the main categories (normal, cognitively impaired, gait impaired and MCR) within the EDSS subgroups. An identical statistical approach was used to determine the differences between the MCR and the EDSS subgroups. A similar statistical analysis was executed to determine the differences between the main categories/MCR subgroup and the disease duration subgroups. All analyses were performed using the SPSS software (version 27.0 for Windows; SPSS Inc., Chicago, Illinois, USA). Reported p values were two-tailed and the level of significance was set at $p < 0.05$.

Results

Demographical and clinical characteristics of the 618 pwMS are summarized in Table 2. Sixty-three (10.2%) patients were diagnosed with MCR, 17.8% ($n = 110$) exhibited only a slow or very slow walking speed, and 15.5% ($n = 96$) exhibited only a cognitive impairment. Fifty-two (out of 96) exhibited a moderate cognitive impairment; 44, a severe cognitive impairment. As for the gait impairment group, 67 and 53 pwMS were classified as slow and very slow walkers, respectively. Demographical and clinical characteristics of all subgroups are detailed in Table 3. The proportions of the four main groups were significantly different between EDSS subgroups. The proportion of subjects categorized as MCR was 26.0% in the severe EDSS subgroup compared with 10.9%, 6.0%, 4.6% in the moderate, mild and very mild EDSS subgroups, respectively (Figure 1). As for the MCR subgroups, 20.0% presented with a severe cognitive impairment co-occurring with a very slow walking speed in the severely disabled subgroup, compared with 12.5% in the moderately disabled subgroup (Figure 2).

The distribution of MCR according to disease duration was inconsistent, although, a larger proportion of pwMS have suffered from MCR or an isolated impairment in gait or cognition for over 20 years from diagnosis. Moreover, 29.2% of pwMS with a disease duration $>$ 20 years were classified as normal, compared with 66.0% of pwMS with a disease duration of up to 1 year. Furthermore, 11.5% of pwMS, 1 year from disease onset, were classified with MCR. Distribution of main groups, and MCR subgroups according to disease duration are illustrated in Figures 3 and 4, respectively.

Table 2. Clinical and demographical information of the study sample according to the main groups (n = 618).

Variable	Total (*n* = 618)	Normal (*n* = 339)	Cognitively impaired (*n* = 96)	Gait impaired (*n* = 110)	MCR (*n* = 63)	*p*-Value
Age (years)	43.7 (12.6)	40.3 (12.2)[a]	39.5 (12.0)[a]	48.8 (12.6)[b]	44.3 (10.9)[a, b]	<0.001
Gender (F/M)	381/237	198/141[a]	73/23[a]	66/54[b]	44/19[a]	0.003
Disease duration (years)	7.5 (9.0)	5.3 (7.5)[a]	7.1 (9.0)[a]	10.8 (10.5)[b]	5.8 (7.1)[a]	<0.001
Type of MS (%RR)	83.8	91.1[a]	89.4[a]	71.2[b]	88[a]	<0.001
Mean EDSS (score)	3.2 (2.0)	1.8 (1.4)[a]	2.9 (1.6)[b]	4.1 (1.8)[c]	3.9 (2.0)[c]	<0.001
Walking speed (m/s)	0.93 (0.30)	1.21 (0.17)[a]	1.13 (0.16)[b]	0.72 (0.17)[c]	0.69 (0.22)[c]	<0.001
Global cognitive score	92.4 (13.4)	101.5 (6.1)[a]	79.7 (8.9)[b]	100.5 (5.8)[a]	78.3 (11.3)[b]	<0.001
Fear of falling (FES-I score)	31.8 (13.2)	22.5 (8.6)[a]	29.2 (12.2)[b]	36.9 (10.9)[c]	39.8 (13.6)[c]	<0.001
Fatigue (MFIS score)	38.8 (22.5)	26.5 (19.2)[a]	41.6 (22.4)[b]	41.5 (19.5)[b]	49.7 (23.3)[b]	<0.001

EDSS, Expanded Disability Status Scale; FES-I, Falls Efficacy Scale International; MCR, motoric cognitive risk; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis.
[a,b,c]are used for post hoc analysis indicating significant differences between the four main groups.

Table 3. Clinical and demographical information of the study sample according to the subgroups.

Variable	Normal (*n* = 339)	Cognitively impaired (*n* = 96)		Gait impaired (*n* = 110)		MCR (*n* = 63)			
	Normal walking speed and cognition	Moderately impaired + Normal walking speed	Severely impaired + Normal walking speed	Slow speed + Normal cognition	Very slow speed + Normal cognition	Slow speed and moderately impaired cognition	Slow speed and severely impaired cognition	Very slow speed and moderately impaired cognition	Very slow speed and severely impaired cognition
n	339	52	44	67	53	19	18	16	10
Age (years)	40.3 (12.2)	39.6 (11.8)	39.3 (12.3)	48.4 (13.3)	49.2 (11.6)	45.1 (11.8)	44.0 (11.8)	46.3 (9.6)	40.0 (10.0)
Gender (F/M)	198/141	41/11	32/12	37/30	29/24	14/5	11/7	11/5	8/2
Disease duration (years)	5.3 (7.5)	7.0 (9.9)	7.3 (8.0)	9.4 (9.9)	12.6 (11.1)	5.8 (8.3)	5.1 (6.3)	7.8 (7.7)	4.4 (5.3)
Mean EDSS (score)	1.8 (1.4)	2.8 (1.5)	3.1 (1.7)	3.5 (1.6)	4.9 (1.7)	3.5 (1.6)	3.3 (2.0)	5.0 (1.6)	4.3 (2.2)
Walking speed (m/s)	1.21 (0.17)	1.14 (0.15)	1.12 (0.16)	0.84 (0.08)	0.57 (0.12)	0.85 (0.06)	0.83 (0.08)	0.46 (0.19)	0.48 (0.14)
Global cognitive score	101.5 (6.1)	86.1 (2.6)	72.1 (7.4)	101.1 (5.7)	99.7 (6.0)	86.1 (2.7)	70.8 (8.1)	85.9 (3.0)	64.9 (13.5)
Fear of falling (FES-I)	22.5 (8.6)	27.6 (11.3)	31.2 (12.9)	32.9 (9.9)	41.8 (10.1)	36.2 (12.7)	34.1 (12.0)	46.1 (12.0)	47.6 (14.2)
Fatigue (MFIS)	26.5 (19.2)	38.3 (19.9)	45.1 (24.6)	33.3 (19.3)	50.7 (15.4)	48.2 (19.0)	36.3 (25.9)	56.1 (22.7)	65.9 (15.2)

EDSS, Expanded Disability Status Scale; FES-I, Falls Efficacy Scale International; MCR, motoric cognitive risk; MFIS, Modified Fatigue Impact Scale.

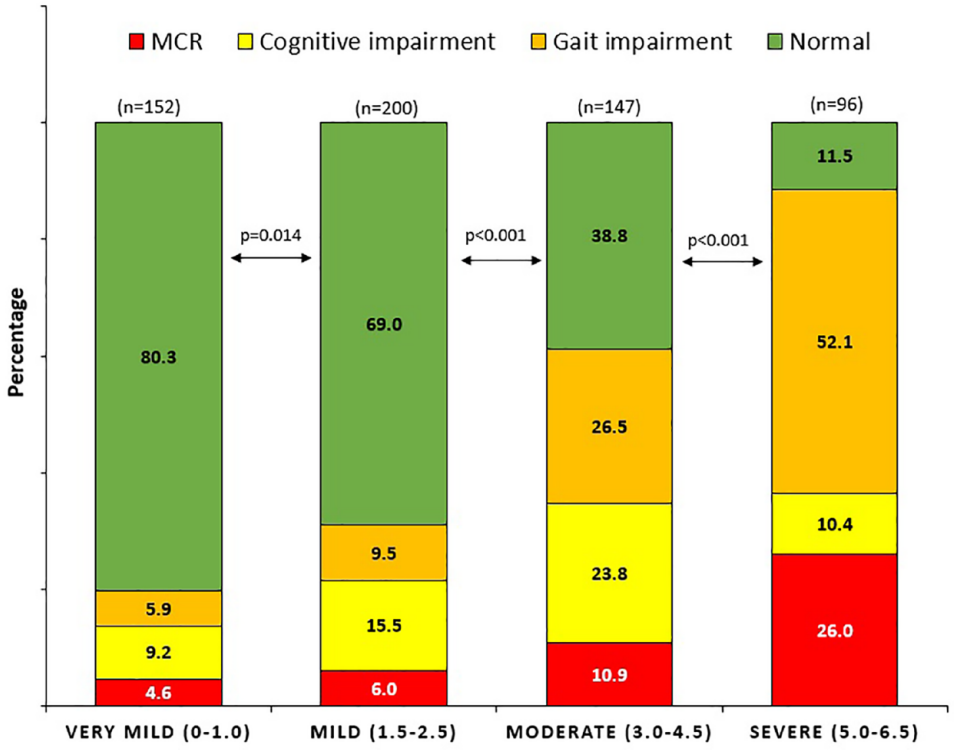

Figure 1. Distribution of the study sample according to main categories and level of disability.

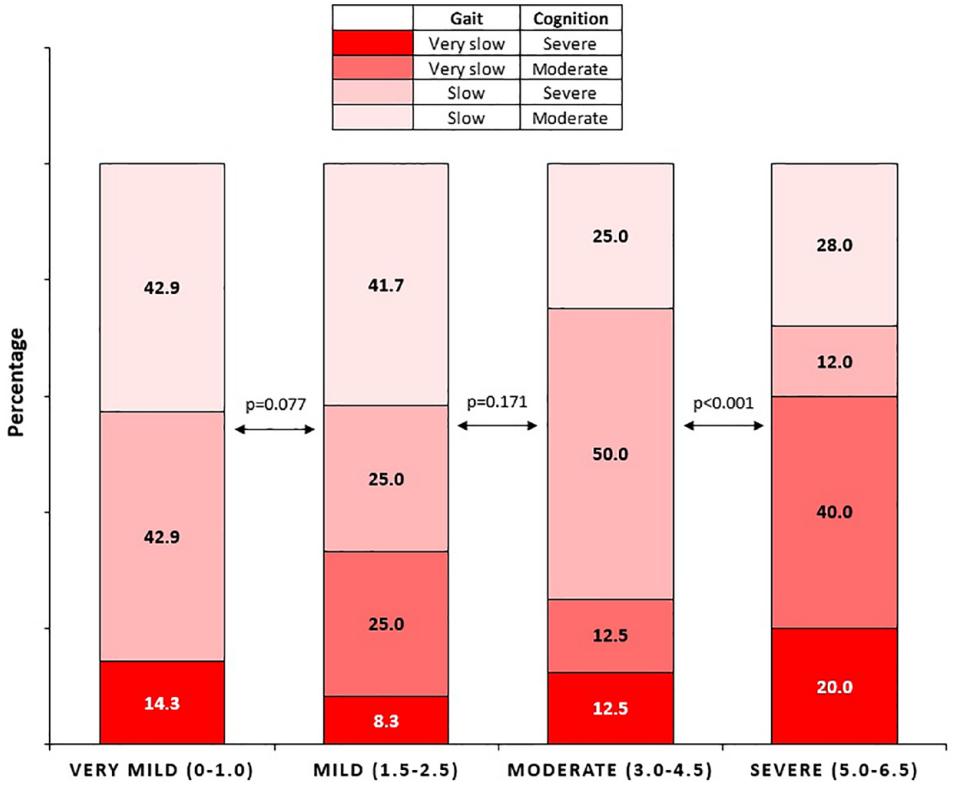

Figure 2. Distribution of the MCR subgroups according to level of disability.

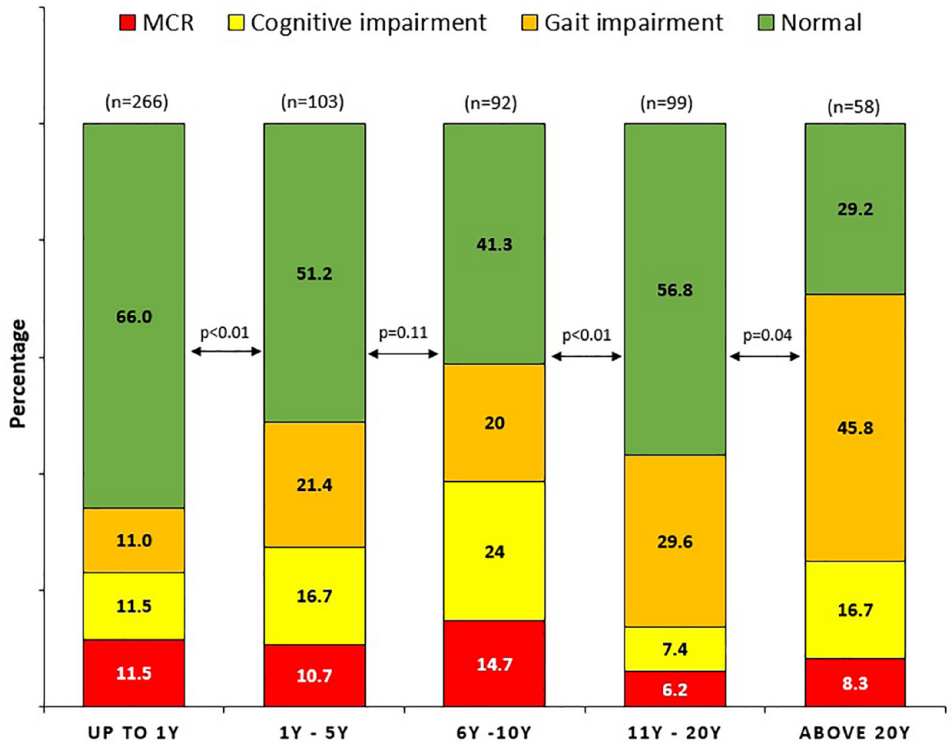

Figure 3. Distribution of the study sample according to main categories and disease duration.

Subjects in the MCR group presented with elevated fatigue compared with patients classified as normal [49.7 (SD = 23.3) vs 26.5 (SD = 19.2), $p < 0.001$]. The mean fatigue score in the MCR group was higher compared with only cognitively and only gait impaired, 41.6 (SD = 22.4), 41.5 (SD = 19.5), respectively, however, the difference was not significant. Fatigue scores according to absolute walking speed and the absolute GCS is presented in Figure 5. Fear of falling was significantly higher in the MCR and gait impairment groups compared with the cognitively impaired and normal groups. FES-I scores (representing fear of falling), according to absolute walking speed and absolute GCS are presented in Figure 6.

Discussion

The primary aim of this study was to examine the prevalence of the MCR syndrome in pwMS. We documented a prevalence of 10.2% cases of MCR. To the best of our knowledge, no prior data have been reported as to the prevalence of MCR in pwMS. We, therefore, compared our score with the 9.7% reported in Verghese *et al*''.s[4] study of 26,802 older adults from 17 countries. Despite the similar prevalence between our MS sample and the older adult's sample, it should be noted that the mean age of participants in Verghese's study was 71.6 years old compared with only 43.7 years old in our pwMS sample, hence, we confidently assume that once cohorts are age-adjusted, the prevalence of MCR in pwMS exceeds that of healthy adults.

To date, there are no data as to the neural mechanisms associated with MCR in pwMS. Nevertheless, we present herein, several studies that have investigated this aspect in older adults.[33–36] Recently, Blumen *et al*'.s sample of 267 older adults (without dementia) demonstrated that the gray matter volume covariance network was associated with MCR. Associations were primarily observed in the cerebellar, inferior temporal, parahippocampal, motor, supplementary motor, insular, and prefrontal cortical brain regions,[33] areas that are linked with control of gait such as motor planning and coordination. Similar findings were reported by Beauchet *et al.*,[34] who linked MCR to brain cortical atrophy in the dorsolateral and prefrontal regions. In contrast, Mergeche *et al.*[35] did not find significant differences in the prevalence of

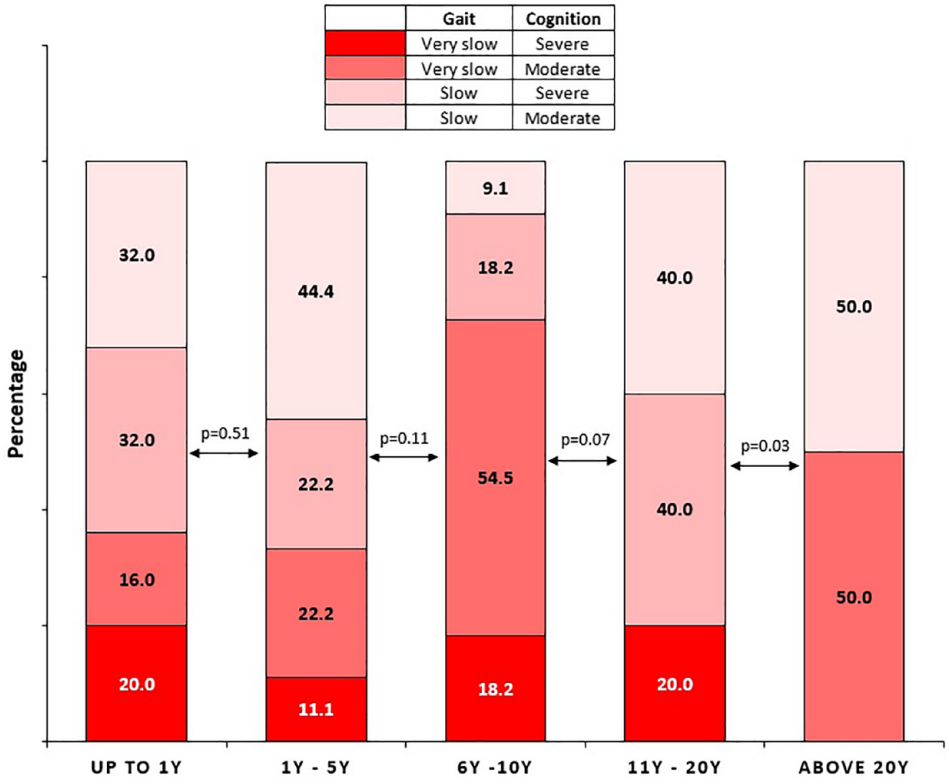

Figure 4. Distribution of the MCR subgroups according to disease duration.

regional white matter hyper intensities between patients with and without MCR, thus, replicating the earlier findings of Wang *et al.*[36] Recently, Yaqub *et al.*[37] reported that MCR is associated with smaller brain tissue volumes, more white matter hypertensities, and a diminished white matter structural integrity, yet, similar associations were found in a study where mild cognitive impairment was found associated with MCR, as well.

There is unlikely to be one unifying mechanism linking MCR with pwMS, nevertheless, we propose several hypotheses. First, the white matter damage, a hallmark of MS, is explicitly related to an increased incidence of MCR (specifically, the slow gait component) in elders.[38] Second, dysfunctions in brain areas such as the supplementary motor and prefrontal cortical brain regions, which are linked with control of gait, i.e. motor planning and coordination, were found both in elders with MCR[33] and pwMS.[39] Finally, the neural mechanism might be explained by the abnormalities in the inflammatory cytokine system. For example, the expression of interleukin (IL)-10 was found associated with an increased incidence of MCR in elders,[40] and associated with low results on cognition tests in relapsing-remitting MS patients.[41] In addition, IL-6, which plays a critical role in the pathogenesis of neural tissue in pwMS,[42] has been found associated with muscle mass reduction, endurance, flexibility, power, and speed in elders.[43] Furthermore, the increased serum cytokine levels of IL-6 serve as prognostic markers for difficulties in mobility.[44] Nonetheless, in order to advance the knowledge of the underlying mechanisms involved with the MCR syndrome in MS, we encourage future longitudinal research, combining gait and cognitive measures with neurophysiological, neuroimaging, or other biomarkers associated with MS.

In addition to examining the prevalence of MCR in pwMS, we explored the relationship between MCR and disability (represented by the EDSS score). The proportion of pwMS categorized as MCR increased in parallel with an increased level of disability. Whereas, the proportion of MCR was 4.6% in very mildly disabled patients, it increased to 10.9% and 26.0% in moderately and severely disabled pwMS, respectively. A similar trend was observed in the gait impairment group. The proportion of pwMS in this group increased from 5.9% in the very mildly disabled

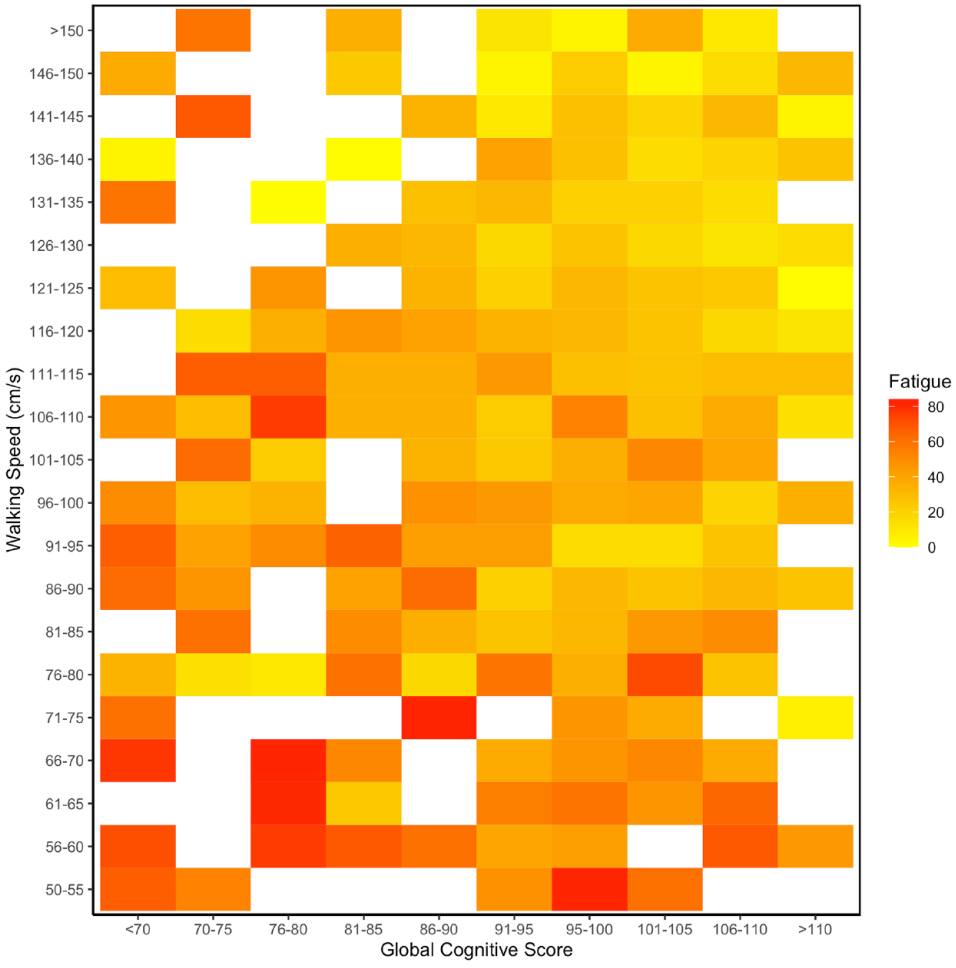

Figure 5. Perceived fatigue according to walking speed and cognition.

patients to 26.5% in the moderately, and 52.1% in the severely disabled subgroups. This finding is not surprising since the EDSS score is largely based on ambulation dysfunction and the use of walking aids. Worth noting, the median EDSS in the MCR and gait impairment groups was identical (=4.0).

In contrast, the prevalence of pwMS categorized with only cognitive impairment, did not follow a similar trend as the MCR and gait impairment groups in relation with the level of disability. The proportion of pwMS demonstrating only cognitive impairment was similar between the severely disabled and very mildly disabled subgroups; 10.4%, 9.2%, respectively. These findings highlight a weakness of the EDSS as a measure of disability in pwMS. The global EDSS score mostly reflects mobility difficulties with less emphasis on cognitive impairments. Therefore, we believe that the MCR is a complementary functional marker of disability in pwMS, as it denotes co-occurrence of cognition and walking impairments.

Another novelty of our study relates to the relationship between MCR and perceived fatigue. We found that fatigue was significantly higher in the MCR group compared with pwMS classified as normal [49.7 (SD = 23.3) vs 26.5 (SD = 19.2)]. Even though the criteria level for significance was not reached, there was a tendency toward elevated perceived fatigue in the MCR group compared with the gait or cognitive impairment group. Worth noting, the majority of studies investigating the MCR syndrome generally divided their samples into two groups: MCR and non-MCR.[1,4,34,35] We used a four-group split, since we believe that it is more informative to

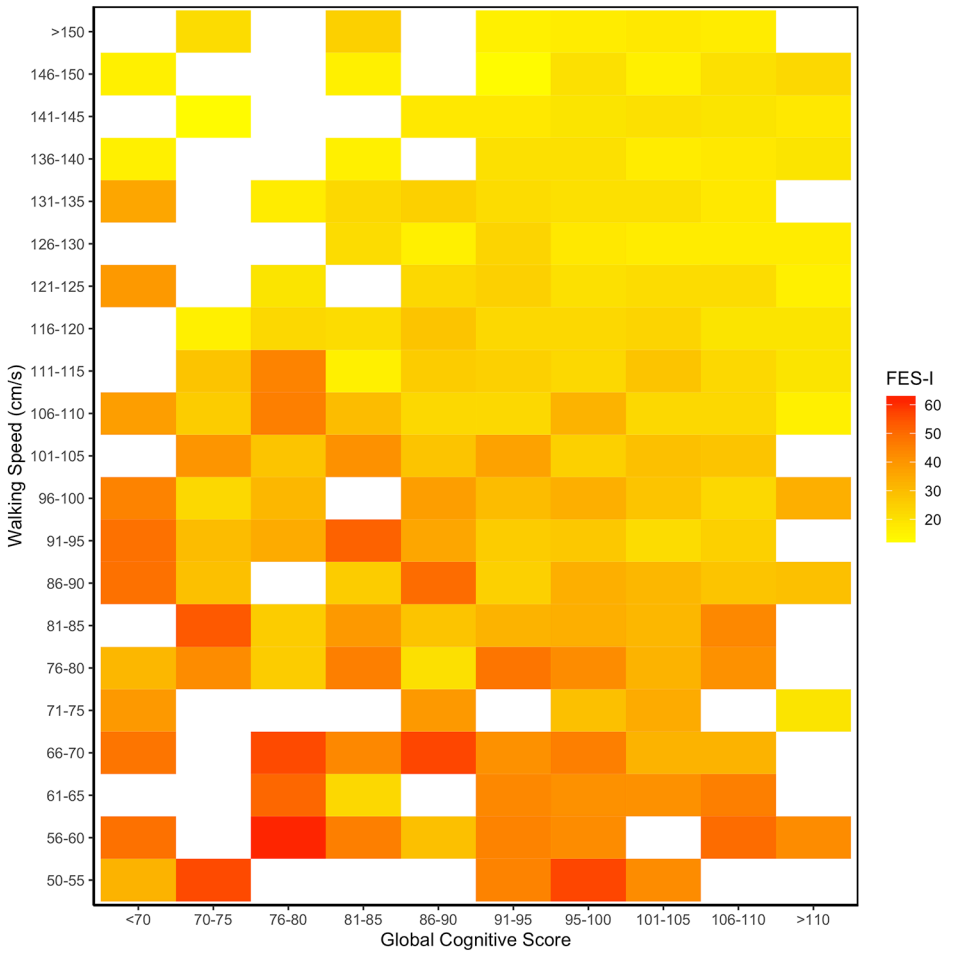

Figure 6. Fear of falling according to walking speed and cognition.

compare the scores of the MCR to those with only cognitive and gait impairment. Theoretically, if our MS cohort was divided according to the MCR/non-MCR categorization, the perceived fatigue score would have been significantly higher in the MCR group.

The inter relationships between walking speed, cognition and perceived fatigue in pwMS are not entirely understood. Previous studies have demonstrated that cognition and perceived fatigue are associated with each other.[45,46] The relationship between walking speed and cognition has been well-documented, predominantly, in studies investigating the cognitive-motor interference in pwMS.[18,47] In contrast, the association between walking speed and perceived fatigue in pwMS is questionable.[48,49] We speculate that since perceived fatigue is a multifactorial construct, it is more frequent, and at a higher level in pwMS who suffer from co-occurring symptoms. For this reason, we feel that the level of fatigue was higher in the MCR group, representing co-occurrence of gait and cognitive impairments compared with the other groups. Notably, we did not analyze the MFIS scores according to its subcategories (i.e. physical, cognitive, and psychosocial functioning), consequently, further research on this issue is still warranted.

Fear of falling was significantly higher in the MCR group compared with the normal and cognitively impaired groups, and slightly higher (under significance level) compared with the gait impaired group. Previous MS studies have reported that impaired gait is associated with a fear of falling;[50,51] others have found it associated with poor global cognition.[52] In a cohort of 540 pwMS, Kalron & Allali found that fear of falling was associated with both poor gait and impaired

cognitive skills,[53] thus, demonstrating an increased fear of falling in pwMS classified with MCR. Hence, we believe that pwMS diagnosed with MCR should be a focus group for future research.

Our study has several strengths. Specifically, this is the first study providing data associated with the MCR syndrome in pwMS. Moreover, the use of computerized cognitive tests enabled us to subcategorize cognitive performance into separate impairment levels. Nevertheless, our study is not clear of limitations. First, our study is cross-sectional, therefore, we were unable to draw definite conclusions as to the development of MCR in pwMS over time. This is especially important for pwMS at the initial stages of the disease as to whether MCR can be used as an early-marker of a more aggressive disease progression. Second, although, the computerized cognitive battery is considered a superior measurement tool compared to a simple yes/no question as to subjective cognitive complaints, specific equipment (and dedicated time) is required, which would subsequently, reduce the simplicity of the MCR syndrome diagnosis. In the same context, subdividing the MCR group into subgroups (based on slow/very slow walking speed and moderate/severe cognitive impairment), does not appear to add significant data vis a vis the standard MCR category, therefore, we question its use for future studies.

We encourage future studies to replicate our study procedures in a new cohort of pwMS by using the original cognitive criteria for MCR as described by Vergherse *et al.*[1] Third, our study did not control all potential confounders associated with cognition (i.e. depression, years of education, anxiety) and/or gait (i.e. spasticity, postural control). Finally, our data are based on a study performed in a single MS center, hence, further data from various MS cohorts are necessary to further clarify the topic of MCR in the MS population.

Conclusions

The current study corroborates the presence of MCR in pwMS. MCR is associated with greater disability, elevated perceived fatigue and increased fear of falling. Furthermore, this syndrome appears throughout all phases of MS. Nevertheless, future research is warranted to better understand its relevance and application. Establishing the neural correlates of MCR in pwMS would improve the awareness of walking and co-occurring cognitive mechanisms involved with the disease, thus, enhancing assessment and rehabilitative strategies. Moreover, a longitudinal research study following the development of MCR in pwMS from disease onset may help determine if this index indicates a unique disease progression.

Ethics approval and consent to participate

The study was approved by the Sheba Institutional Review Board Ethics Committee (Ethics Ref: 5596-08/141210) with a full exemption of written or verbal consent from the study participants.

Consent for publication

Not applicable.

Author contributions

Sapir Dreyer-Alster: Data curation; Formal analysis; Writing – review & editing.

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Conflict of interest statement

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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