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Interplay Between Cognitive and Bowel/Bladder Function in Multiple Sclerosis

Running Title: Cognition and Sphincter Dysfunction in MS

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ABSTRACT

Purpose: to evaluate the prevalence of bowel/bladder dysfunction in multiple sclerosis (MS) and the association with cognitive impairment.

Methods: We prospectively enrolled 150 MS patients. Patients were administered the Symbol Digit Modality Test (SDMT), and filled the Neurogenic Bowel Dysfunction Score (NBDS) and the Actionable Bladder Symptom Screening Tool (ABSST). Association between bowel/bladder dysfunction and cognitive function was assessed through hierarchical regression models using SDMT and clinic-demographic features as independent variables and NBDS or ABSST score as dependent variables.

Results: Prevalence for bowel/bladder deficit was 44.7%, with 26 patients (17.3%) suffering from bowel deficits and 60 patients (40%) from bladder deficits. Total NBDS and ABSST correlated with SDMT (coeff. = -0.10, $p<0.001$ and coeff. = -0.03, $p=0.04$, respectively) after correction for demographic features and physical disability.

Conclusions: Bowel/bladder disorders are common in MS and are associated with both physical and cognitive disability burden. As SDMT is embedded into routine clinical assessment, a lower score may warrant investigating bowel/bladder dysfunction due their strong interplay.

Keywords: Bowel; Bladder; Cognition; Disability; Patient reported outcome

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INTRODUCTION

Multiple Sclerosis (MS) is a disabling immune-mediated disorder of the central nervous system mostly affecting young adults. MS-related physical disability has a negative impact on quality of life and harshly affects both social and economic patients' life [1, 2]. MS-related symptoms encompass a wide variety of deficits including, but not limited to, visual disturbances, motor weakness, sensory changes and ataxia. Bowel/bladder deficits, such as retention or incontinence, are also detected in about 52-97% of MS patients and are conventionally thought to be associated with spinal cord pathology [3, 4]. Although these symptoms are extremely distressing and impact patients' social and working life [5], patients are usually reluctant to discuss them due to the embarrassing nature of the matter [6]. In addition, clinicians do not always ask for bowel and bladder dysfunction because of the limited timeframe for the clinical assessment, increasing the underestimation of bowel/bladder disorder in MS patients. Therefore, there is a need for clinical clues and screening tools for bowel/bladder dysfunction in MS. This is especially true when considering that when correctly diagnosed, bowel/bladder dysfunction may benefit from a variety of symptomatic treatments, such as anticholinergic drugs, desmopressin, intermittent self-catheterization, cannabinoids, detrusor injections of botulinum neurotoxin type A and surgical management [7].

Cognitive functions are thought to play a key role in controlling bowel/bladder function in healthy subjects [8]. Patients affected by impaired cognitive functions caused by neurological conditions such as vascular dementia and Parkinson's disease also display issues in controlling bowel and bladder function [9, 10]. The association between cognitive performances and bowel/bladder control may depend upon the strong overlap of brain structures activated by both functions, namely, the prefrontal cortex, the thalamus, the cerebellum and the brainstem [11, 12]. As cognitive impairment can be detected in up to 75%

of MS patients [13, 14], mostly affecting processing speed, attention, executive functioning and working memory [13, 15], we may hypothesize that cognitive impairment may be a red flag for bowel/bladder dysfunction in MS, as for other neurological condition.

Thus, with this study we aim to (i) estimate the prevalence for both bowel and bladder dysfunction in MS (ii) evaluate their association with cognitive function.

MATERIALS AND METHODS

Subjects Enrolment

In this cross-sectional study, patients diagnosed with MS according to the 2017 McDonald's criteria [16] were prospectively and consecutively enrolled at the MS centre of "Federico II" University of Naples (Italy) between September and December 2019. Inclusion criteria were: i) age between 18 and 65 years old ii) Expanded Disability Status Scale (EDSS) $\leq$ 7.5. We excluded patients with i) any disorder other than MS leading to bowel/bladder dysfunction (i.e. major malformations, major cardiovascular risk factors, other major psychiatric conditions); ii) patients with concomitant treatments that may lead to bowel/bladder dysfunction (i.e. antidepressants, verapamil or beta-blockers); iii) clinical relapse in the 6 months preceding screening clinical history.

For each patient, we collected clinical and demographic data, including the assessment of physical disability through the EDSS and the bowel/bladder subscale, educational level, treatment status, and disease course. In order to disentangle real bowel/bladder incontinence from incontinence related to limited mobility, we divided patients according to the extent of physical disability in fully ambulatory patients (EDSS $\leq$ 4.0) and patients with ambulation restrictions. Finally, to globally assess patients' cognition, we administered the Symbol Digit Modality Test (SDMT), as it is widely accepted as a screening tool for cognitive impairment in MS [17, 18].

The study was approved by the Institutional Review Board of the University of Naples 'Federico II' and all investigators adhered to the tenets of the Declaration of Helsinki. Written informed consents were obtained from all subjects enrolled in the study.

Neurogenic Bowel Dysfunction Score

Each patient filled in the self-administered Neurogenic Bowel Dysfunction Score (NBDS) questionnaire to assess bowel functions [19]. NBDS is a 10-item multiple choice questionnaire assessing frequency of bowel movements, headache, perspiration or discomfort during defecation; use of medication for constipation or fecal incontinence; time spent on defecation; frequency of digital stimulation or evacuation; frequency of fecal incontinence; flatus; and perianal skin problems. For each item a score for the selected answer is assigned and a total score can be calculated by summing the scores for each answer. Total score can be converted on a 'very low-low-moderate-severe' neurogenic bowel dysfunction. NBDS has been validated in MS [20] and is widely used as primary outcome in trials assessing the impact of treatment on bowel function [21]. Patients were classified as having bowel dysfunction for total NBDS $\geq$ 10. In addition, each patient also completed a 0 to 10 Numerical Rating Scale (NRS) for bowel function satisfaction with 10 representing the maximal satisfactory level.

Actionable Bladder Symptom Screening Tool

Actionable Bladder Symptom Screening Tool (ABSST) was administered to each patient. As the NBDS, also the ABSST is a self-administered questionnaire. It is a short 8-item questionnaire specifically designed to assess bladder function in MS patients [22, 23]. Each item is scored on a scale from 0 to 1 (0 = None of the time, 0 = Some of the time, 1 = Most of

the time and 1 = All of the time) and the scores achieved for each single item are summed up to the total score. A total score equal or higher than 3 warns for bladder dysfunction [22, 23].

Statistical Analyses

Statistical analyses were performed using Stata software (version 13; StataCorp LP, College Station, TX). Demographic and clinical features are presented as means, medians or proportions, as appropriate. Between-groups comparison was performed using Student's t-test or ANOVA as appropriate. Pairwise correlations were assessed through Pearson's correlation test. In order to evaluate the additional impact of cognitive function on bowel and bladder dysfunction over and above demographic features and physical disability status we applied three separate hierarchical linear regression procedures using alternatively NRS for bowel function or NBDS or ABSST scores as dependent variables. In the first step, demographic variables (age, gender and education) were entered into the models. The second step added the illness-related variables (physical disability status, disease course, disease duration, annualised relapse rate), and the third step added SDMT score. Nagelkerke R^2 for each model will be reported. Normal distribution of variables and residuals were evaluated with Shapiro-Wilk test and graphical approaches. Results were considered statistically significant for $p<0.05$.

RESULTS

We enrolled 150 MS patients (91 female and 59 male) with a mean age of 43.3 ± 11.5 years and mean disease duration of 11.8 ± 7.6 years. Demographic and clinical data are summarised in Table 1. All patients had SDMT, NBDS and ABSST data. Scores for each test are summarized in Table 2.

Overall, prevalence for bowel or bladder deficit was 44.7%, with 26 patients out of 150 (17.33%) suffering from bowel deficits, and 60 out of 150 patients (40%) from bladder deficits. Nineteen out of 150 MS patients (12.7%) presented both bowel and bladder dysfunction. Patients with bowel/bladder deficits were not different for gender compared with MS patients without deficits but they had older age (46.7 ± 10.7 vs 40.6 ± 11.4, p=0.001), higher EDSS (4.54 ± 1.52 vs 3.17 ± 1.83, p<0.001), progressive course of the disease (58.2% vs 41.8%, p=0.002), and lower SDMT score (34.6 ± 19.3 vs 45.1 ± 16.5, p<0.001).

NRS for bowel function did not differ between male and female and between relapsing or progressive disease course whilst it was higher in fully ambulatory patients compared to patients with ambulation restriction (7.72 ± 2.31 vs 6.10 ± 2.73, p<0.001). NRS for bowel function correlated with age (r=-0.25, p=0.004), disease duration (r=-0.29, p<0.001), EDSS (r=-0.43, p<0.001) and SDMT (r=0.23, p=0.003). NRS for bowel function did not differ according to bowel/bladder EDSS subscale score (See Figure 1a).

Total NBDS did not differ between male and female and between relapsing or progressive disease course whilst it was lower in fully ambulatory patients compared with patients with ambulation restriction (3.33 ± 5.35 vs 7.04 ± 7.55, p<0.001). Total NBDS correlated with age (r=0.23, p=0.005), disease duration (r=0.16, p=0.04), EDSS (r=0.39, p<0.001) and SDMT (r=-0.43, p<0.001). Total NBDS differed according to bowel/bladder EDSS subscale score (p<0.001, See Figure 1b).

ABSST total score did not differ for gender and disease course whilst it was lower in fully ambulatory patients compared with patients with ambulation restriction (2.06 ± 2.54 vs 4.18 ± 2.93, p<0.001). ABSST total score correlated with age (r=0.31, p<0.001), EDSS (r=0.45, p<0.001) and SDMT (r=-0.36, p<0.001). ABSST total score differed according to bowel/bladder EDSS subscale score (p=0.04, See Figure 1c). ABSST total score correlated with both total NBDS (r=0.53, p<0.001) and NRS for bowel function (r=-0.46, p<0.001).

On hierarchical regression models, after correction for physical disability, demographic features and disease course, NRS for bowel function only correlated with disease duration (coeff. = -0.08 95% CI= -0.14 – -0.02, p=0.013). Both total NBDS and ABSST total score correlated with SDMT (coeff. = -0.10 95% CI= -0.18 – -0.02, p<0.001 and coeff. = -0.03 95% CI= -0.06 – -0.01, p=0.04, respectively, see Table 3 and Figure 2), after correction for physical disability, demographic features and disease course.

DISCUSSION

In this study, we showed that about 45% of MS patients experience bowel/bladder symptoms throughout their disease course. Bowel/bladder dysfunction was associated with older age, progressive MS course and higher physical disability. We also demonstrated that both bowel and bladder dysfunctions are associated with impaired cognition independently from the extent of physical disability and disease course.

The main finding of the present study is the interplay between cognition and bowel/bladder function in MS independently from physical disability. Cognitive impairment can affect up to 75% of MS patients [13, 14] and is associated with physical disability and limited mobility in MS [24], which can, in turn, affect bowel/bladder function. For example, patients with limited mobility may complain about incontinence because they are not able to reach the bathroom on time. Therefore, in order to take into account physical disability when evaluating the association between cognition and bowel/bladder function we evaluated the impact of cognition over and above physical disability and demographic features through the hierarchical regression model, thus adjusting for these factors. The association between SDMT and bowel/bladder function still remained significant, with patients suffering from impaired cognition showing worse bowel/bladder control. From the neuropsychological point of view, Harvey et al. already described the influence of cognition on bladder voiding

elaborating the concept of 'cognitive voiding' [25], showing that subjects aware of bladder filling integrate this information with other factors including temporal map, voiding behaviour and habituation in order to decide when and where to void [25]. Specifically, attention and information processing speed are essential in integrating the awareness of bowel and bladder filling and the possibility/impossibility to void depending on the context. To strengthen the concept of cognitive voiding, it has been demonstrated that cognitive rehabilitation programs aimed at reinforcing dual task abilities and attention focus are able to improve also bowel/bladder function [26, 27].

The association between cognition and bowel/bladder function may also rely on the common neurological pathways controlling both functions. As for attention and information processing explored through the SDMT, bowel/bladder function is associated with structural integrity and functional activation of different structures throughout the central nervous system, namely, the frontal lobes, brainstem, cerebellum, thalamus and temporo-parietal lobes and white matter bundles connecting prefrontal cortex to subcortical structures [28-33]. However, MRI studies exploring both bowel/bladder and cognitive functions are required in order to evaluate whether lesion location, resulting in disconnection between brain regions, or neurodegeneration of selective cortical areas are relevant for both functions in MS patients. These studies will not only provide information about pathological anatomical substrates underpinning bowel/bladder dysfunction but will also be useful to design rehabilitation program aimed at increasing activation in selected brain regions, perhaps through transcranial magnetic simulation.

Another finding from the present study is the prevalence for bowel/bladder dysfunction in MS that we detected in about 45% of our MS sample. Specifically, 26 patients out of 150 (17.33%) displayed bowel deficits and 60 out of 150 patients (40%) presented with bladder deficits. Previous studies reported a prevalence from 50 to 95% for bladder deficits and a

prevalence from 12 to 32 % for bowel deficits [7, 34]. The wide prevalence range for both bladder and bowel dysfunction accounts for several factors. Firstly, bowel/bladder dysfunction is very difficult to be diagnosed as patients may complain of various and heterogeneous symptoms due to an impaired storage or voiding process that may not be directly related to MS if not after proper bowel/bladder assessment. Thus, the absence of a multidisciplinary team in the clinical frame may underestimate the prevalence of bowel/bladder dysfunction. Secondly, patients themselves do not associate bowel/bladder dysfunction to MS and do not report the symptoms to clinicians. Patients may not seek help for their bowel/bladder symptoms as they are reluctant to talk about them to clinicians for the social stigma surrounding the topic [6]. Lastly, there is no world-wide consensus on the screening tool to be used to assess bowel/bladder function. Therefore, there is an urgent need for adopting a common screening tool in order to calculate prevalence for bowel and bladder disorder in MS and to introduce these tools as outcome for trials aimed at treating sphincter disturbances. However, a large Italian study, reported a prevalence for bladder deficit of 42% and a prevalence for bowel deficit of 11% [35]. This finding is in line with our data and confirms that our population is representative of the Italian population, thus reinforcing our finding about the correlation between cognition and bowel/bladder dysfunction. As a matter of fact, the tools we used in the present study, namely the NBDS and ABSST, are aimed at screening bowel/bladder deficits but they are not able to disentangle these disorders (i.e. whether this is due to overactive bladder or urgency urinary incontinence or sphincter dysfunction). Therefore, new studies aimed at assessing the relationship between cognition and each specific bowel/bladder disorder, would shed further light on the topic.

In conclusion, we demonstrated that bowel/bladder disorders are common in MS and are associated with both physical and cognitive disability burden. As the prevalence is quite high but patients are reluctant to report on sphincter symptoms, a self-administered screening

questionnaire may facilitate their detection. Moreover, as SDMT is becoming more and more embedded into the clinical assessment routine, a lower SDMT score should warrant clinicians investigating bowel/bladder dysfunction, due to the strong interplay between these two domains. Early identification of sphincter dysfunction in MS is helpful for clinicians to evaluate tailored treatment strategies. Finally, future imaging studies may evaluate common pathological substrates for cognitive and sphincter dysfunction in order to design tailored rehab treatment stimulating activation of selected cortical areas, perhaps through transcranial magnetic stimulation or through cognitive task reinforcing specific cognitive domains.

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Figure legend

Figure 1. Bowel/bladder dysfunction as assessed through the EDSS subscales, NBD and Actionable MS Incontinence Screening Tool total score.

Box and whiskers plot displays median, 5-25-75-95th percentiles for Numerical Rating Scale (NRS) for bowel function (a), total Neurogenic Bowel Dysfunction Score (NBDS) (b) and Actionable Bladder Symptom Screening Tool (ABSST) total score (c). *$p<0.05$, **$p<0.001$ after Bonferroni correction.

Figure 2. Association between bowel/bladder dysfunction and cognition.

Scatter plots show the association between SDMT and both total Neurogenic Bowel Dysfunction Score (NBDS) (a; coeff. = -0.10, $p<0.001$) and Actionable Bladder Symptom Screening Tool (ABSST) total score (b; coeff. = -0.03, $p=0.04$).

Table 1. Demographic and clinical data of the sample

Characteristic		
Subjects		150
Gender	Male, N (%)	59 (39.3)
	Female, N (%)	91 (60.7)
Age, mean ± SD (Range) (years)		43.3 ± 11.5 (18 - 65)
Education, median (Range) (years)		13 (0 - 18)
EDSS, median (Range)		3.5 (0 – 7.5)
Ambulation status	Fully Ambulatory, N (%)	101 (67)
	Ambulation restriction, N (%)	49 (33)
Disease Duration, median (Range) (years)		10.5 (0 - 40)
Annualized Relapse Rate, median (Range)		0.37 (0 - 2)
Disease Course	Relapsing-Remitting, N (%)	108 (72)
	Secondary-Progressive, N (%)	36 (24)
	Primary-Progressive, N (%)	4 (6)
Disease Modifying Treatment	No treatment, N (%)	1 (0.7)
	IFNβ, N (%)	21 (14)
	Glatiramer acetate, N (%)	5 (3.3)
	Dimethyl fumarate, N (%)	13 (8.7)
	Fingolimod, N (%)	15 (10)
	Cladribine, N (%)	1 (0.7)

	Natalizumab, N (%)	38 (25.3)
	Teriflunomide, N (%)	6 (4)
	Alemtuzumab, N (%)	19 (12.7)
	Ocrelizumab, N (%)	22 (14.7)
	Rituximab, N (%)	7 (4.7)
	Siponimod, N (%)	2 (1.2)

Table 2. Results from Bowel, Bladder questionnaires and cognitive function.

Test		**Reference Score**
Neurogenic Bowel Dysfunction (Numerical Rating Scale), mean ± SD	7.24 ± 2.55	0 - 10
Neurogenic Bowel Dysfunction (Total Score), mean ± SD	4.54 ± 6.38	0 - 47
Neurogenic Bowel Dysfunction, Disability level	Very Low, N (%) 110 (73.3)	0 - 6
	Low, N (%) 14 (9.3)	7 - 9
	Moderate, N (%) 10 (6.7)	10 - 13

	Severe, N (%)	16 (10.7)	14 - 47
Actionable MS Incontinence Screening Tool score, mean ± SD		2.70 ± 2.83	0 - 8
SDMT, mean ± SD		40.42 ± 18.51	0 - 110

SD= standard deviation; SDMT=Symbol Digit Modalities Test.

Table 3. Prediction of Neurogenic Bowel Dysfunction total score and Actionable MS Incontinence Screening Tool score.

Neurogenic Bowel Dysfunction total score				
		Nagelkerke R^2	**R^2 change**	**p Value for change**
First step		0.11	-	-
Second step		0.17	0.06	0.09
Third step		0.21	0.04	0.01*
Variables (third step)	**Coefficient**	**95% Conf. Interval**	**Beta Coeff.**	**p Value**
Female vs Male	0.47	-1.55 - 2.50	0.04	0.65
Age	-0.03	-0.14 - 0.08	-0.06	0.58
Education (years)	-0.16	-0.45 - 0.14	-0.10	0.29
Patients with ambulatory restriction vs fully ambulatory	0.21	-2.66 - 3.08	0.02	0.88
Secondary Progressive vs Relapsing Remitting	1.99	-1.12 - 5.09	0.13	0.21
Primary Progressive vs Relapsing Remitting	1.40	-4.16 - 6.96	0.04	0.62
Disease duration	0.07	-0.08 - 0.22	0.08	0.36
Annualized Relapse Rate	0.07	-2.51 - 2.65	0.00	0.96
SDMT score	-0.10	-0.18 - -0.02	-0.30	0.01*
Actionable MS Incontinence Screening Tool score				
		Nagelkerke R^2	**R^2 change**	**p Value for change**
First step		0.09	-	-
Second step		0.16	0.06	0.06

Third step		0.18	0.03	0.03*

Variables (third step)	**Coefficient**	**95% Conf. Interval**	**Beta Coeff.**	**p Value**
Female vs Male	0.03	-0.89 - 0.94	0.00	0.96
Age	0.02	-0.03 - 0.07	0.10	0.35
Education (years)	-0.18	-0.32 - 0.08	-0.12	0.24
Patients with ambulatory restriction vs fully ambulatory	1.23	-0.14 - 2.60	0.20	0.08
Secondary Progressive vs Relapsing Remitting	-0.07	-1.53 - 1.39	-0.01	0.92
Primary Progressive vs Relapsing Remitting	0.73	-1.80 - 3.26	0.05	0.57
Disease duration	-0.01	-0.08 - 0.06	-0.03	0.76
Annualized Relapse Rate	-0.49	-1.66 - 0.68	-0.07	0.41
SDMT score	-0.03	-0.06 - 0.01	-0.21	0.04*

SDMT=Symbol Digit Modalities Test; *=p value<0.05.

Figure 1

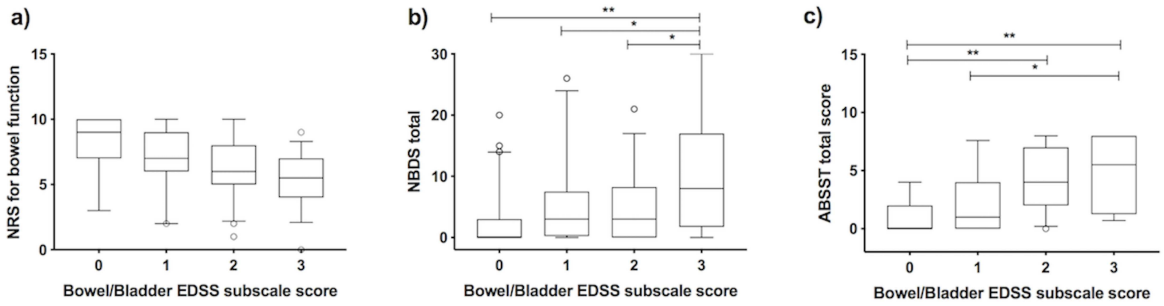

Figure 2