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RESEARCH ARTICLE

Dysphagia assessment in patients with multiple sclerosis – an additional piece to disability burden

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Abstract

Objective: People with multiple sclerosis (MS) might experience symptoms that are usually underestimated. Dysphagia should be evaluated within the Expanded Disability Status Scale (EDSS), but clinicians often do not assess it properly. The objectives of this study are as follows: To assess the prevalence of dysphagia in patients with MS utilizing the Swallowing Disturbance Questionnaire (SDQ); to examine the correlation with the EDSS; to investigate the relationship between dysphagia and clinico-demographic characteristics of MS. **Methods**: In total, 177 MS patients underwent evaluations with EDSS, SDQ, cognitive functions, anxiety, depression, fatigue, and sleep quality tests. We compared clinico-demographic data of patients with and without dysphagia and native-EDSS to SDQ-EDSS. **Results**: Out of the 177 MS patients, 56% of individuals were identified having dysphagia according to the SDQ with 41 patients exhibiting mild dysphagia, 31 showing moderate dysphagia and 27 patients having severe dysphagia. Only 6 patients had dysphagia recorded in the EDSS. SDQ-EDSS scores were significantly higher than native scores. Dysphagia was associated with depressive symptoms and sleep quality. **Interpretation**: Dysphagia affects up to 56% of MS patients. The SDQ questionnaire is useful for identifying dysphagia, which can help in capturing disease progression and preventing complications like aspiration pneumonia. The SDQ-EDSS was higher than the native-EDSS, reflecting the poor ability of the native-EDSS to evaluate certain symptoms such as dysphagia. The SDQ correlated with depressive symptoms, which are associated with a greater perception of MS symptoms, and poor sleep quality, which could be associated with the triggering of pathogenic mechanisms responsible for disease progression.

Introduction

Multiple sclerosis (MS) is the most prevalent nontraumatic debilitating condition impacting young adults.[1] Besides overt motor disability, assessed through the Expanded Disability Status Scale (EDSS),[2] individuals affected by MS may experience symptoms that are not conventionally recorded in clinical practice. These symptoms are often referred to as "invisible" and include cognitive impairment, fatigue, alterations in mood, physical and emotional discomfort, gastrointestinal and urinary disturbances, and sexual dysfunction.[3] Invisible symptoms may exert a greater influence on patients' quality of life (QoL) irrespective of changes in the EDSS.[3] Dysphagia is one of the MS symptoms often going unnoticed.[4] Swallowing difficulties are prevalent in MS, impacting over one-third of patients.[5] Although dysphagia is included in the assessment of the EDSS, due to the limited time for clinical assessment in clinical practice, its prevalence might be underestimated. Consequently, this could lead

to an underestimation of the EDSS and, of utmost importance, to a severe life-threatening complication such as aspiration pneumonia. Recently, the Italian 14-item swallowing disturbance questionnaire (SDQ) has been tested as a new assessment tool for dysphagia for people with MS,[6] showing high consistency. Since the previous study was aimed to validate the questionnaire, SDQ was only applied to patient with long disease duration and a high rate of disability, thus limiting the generalizability of the results to the real-world MS population with greater variability in the extent of disability. Furthermore, in the previous study, the SDQ's impact on the EDSS was not evaluated. Against this background, in this study, we aim to assess the prevalence of dysphagia in MS patients and to characterize dysphagia depending on liquids or solids. We also aimed to assess the associations of dysphagia with clinical and demographic characteristics of people with MS and evaluate the impact of dysphagia assessed through SDQ on the EDSS. We would anticipate that prevalence of dysphagia would be around 30% based on previous studies with an underestimation of dysphagia in the EDSS assessment.

Materials and Methods

Study design and population

This was a mono-centric cross-sectional study. We included consecutive MS patients at MS Clinical Care and Research Centre of the Federico II University Hospital of Naples, Italy, satisfying the following inclusion criteria: (1) MS diagnosis according to the 2017 McDonald criteria[7] with both relapsing or progressive disease course; (2) age > 18 years old and lower than 66 years as to avoid other conditions eventually impacting swallowing abilities such as edentulous state; (3) no other diseases or conditions causing swallowing problems, such as thyroid goiter, systemic autoimmune diseases, mobile dentures, or other orthodontic appliances; (4) disability status assessed through the Expanded Disability Status Scale (EDSS) lower than 7.5; (5) no history of significant medical illnesses, fever or substance abuse in the 30 days before sample collection; (6) stable for at least 6 months under disease-modifying treatment and no clinical relapse in the last 30 days.

Clinical assessment

At baseline we recorded clinical and demographic data [i.e., age, sex, disease duration (time from disease diagnosis to study visit), on-going disease-modifying treatment, smoking status, and disease descriptors]. Each patient underwent a clinical examination, including the assessment of physical disability through the EDSS[2] including the scores at the six functional systems (FS) according to the Neurostatus definitions from trained and certified examiners (RL, AC, MM, VBM, and MP) with more than 10 years of EDSS examination experience blinded to whether patients were included or not in the trial and before SDQ was administered. SDQ was administered on the same day of EDSS assessment.

Neuropsychometric assessment

One hundred and sixty-three patients out of the 177 participants underwent a comprehensive cognitive and psychometric assessment. We lack cognitive assessment for 14 patients because 10 of them did not carried glasses with them and 4 refused to complete the whole assessment for discomfort. Cognitive function was evaluated using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). The BICAMS battery assesses attention, information processing speed, working memory, and verbal and visual memory, which are commonly impaired in MS patients. Specifically, BICAMS battery encompasses the Symbol Digit Modalities Test (SDMT) to assess attention, information processing speed, and working memory, the California Verbal Learning Test-II (CVLT-II) and the Brief Visuo-spatial Memory Test (BVMT) to assess verbal and spatial memory, respectively. Scores were adjusted for age, gender, and education according to Italian normative values, with corrected scores below 35 indicating impairment at the specific test[8]. The total cerebral functional score (CFS) was calculated as the sum of impaired cognitive domains, with patients scoring higher than 0 classified as cognitively impaired. Additionally, each patient completed the Italian versions of Beck's Depression Inventory-II (BDI-II),[9] Beck Anxiety Inventory (BAI)[9] to assess depressive and anxiety symptoms, respectively, the Modified Fatigue Impact Scale (MFIS),[10] which provides scores for cognitive, physical, and psychosocial fatigue, and the Pittsburgh Sleep Quality Index (PSQI)[11] to assess sleep quality. Patients with severe cognitive impairment (CFS = 3) we asked caregivers to assist with BDI-II, BAI, MFIS, PSQI, and SDQ assessment.

Dysphagia assessment

Each patient underwent dysphagia assessment using the Italian version of the SDQ, a 15-item questionnaire designed to evaluate symptoms of dysphagia during the oral and pharyngeal stages.[6] It comprises 5 questions (Items 1–5) related to oral-stage symptoms and 10 questions (Items 6–15) concerning pharyngeal-stage symptoms. Questions 1–14 are rated on a 4-point scale to indicate the frequency of symptoms:

- 0 – "never";
- 1 – "rarely" (≥ once per month);
- 2 – "often" (1–7 times per week);
- 3 – "very often" (>7 times per week).

The 15th question has binary response options of "yes" or "no."

According to the validation study, patients with a total SDQ score equal to zero were classified as not having dysphagia, patients scoring between 1 and 3 were classified as having mild dysphagia, patients scoring between 4 and 8 were classified as having moderate dysphagia. Finally, patients scoring higher than 8 at SDQ were classified as having severe dysphagia.[6] Although the DYMUS questionnaire is specifically designed for assessing dysphagia in MS patients,[12] it presents some limitations as it does not address dysphagia for saliva or different food textures like pureed food and it only allows for a dichotomous response (yes/no) without staging the frequency of dysphagia symptoms as it was underlined.[6]

Statistical analysis

Statistical analyses were performed using the Stata/MP software (version15.03; StataCorp LP, College Station, TX, USA). Demographic and clinical features of study subjects are presented as means, medians, or proportions as appropriate. All demographic and clinical and laboratory variables were checked for normality using the Shapiro–Wilk normality test and graphical approaches.

Clinico-demographic differences between patients with and without dysphagia were assessed through unpaired two-tailed *t*-test, Wilcoxon rank-sum test and chi-square as appropriate.

Correlation between SDQ total score and clinico-demographic features were assessed through backward stepwise regression analysis using SDQ total score as dependent variable and age, sex, disease duration, disease course, smoking habits, EDSS, CFS, BDI, MFIS total score and MFIS subscores, BAI total score, and PSQI total score as predictors using $P = 0.20$ as the critical value for removing the variables from the model. Native-EDSS and SDQ-EDSS (i.e., EDSS corrected for the SDQ assessment) as well as native brainstem FS and SDQ-brainstem FS were compared using the paired *t*-test. As the addition of SDQ to total EDSS calculation is able to influence only patients with native-EDSS ≤ 4.0 as for EDSS definition, we repeated the same analysis only in the subgroup of MS patients with EDSS lower than 4.5. In order to unveil clinico-demographic variables affecting native-EDSS/SDQ-EDSS discrepancy if any, we performed a stepwise backward logistic regression analysis using age, sex, disease duration, smoking habits, disease course, native-EDSS, CFS, BDI, MFIS total score, BAI, PSQI score as covariates and native-EDSS/SDQ-EDSS discrepancy as dependent variable using $P = 0.20$ as the critical value for removing the variables from the model.

A $P < 0.05$ was considered statistically significant. Results are presented with 95% confidence interval (95% CI) or *P* values.

Results

Clinical measures at baseline

We enrolled 117 females (66%) and 60 males (34%) with a mean age of 46.1 ± 11.1 years, a median disease duration of 13 (0–34) years and a median EDSS of 3.0 (1.0–7.0). Most of the patients were relapsing–remitting (65%), although we also enrolled 61 progressive MS patients (35%). Demographic and clinical data, including cognitive and neuropsychological features from subjects enrolled in the study are summarized in Table 1. Eighty-three patients out of 163 (51%) showed different degrees of cognitive impairment whilst 80 patients (49%) did not present with any cognitive changes.

Dysphagia assessment

Using the SDQ questionnaire, we showed that 99 patients (56%) have dysphagia with 41 patients (23%) having mild dysphagia, 31 (18%) having moderate dysphagia, and 27 patients (15%) having severe dysphagia. Mean total score was 3.77 ± 6.08. The number and percentage of patients answering between 1 and 3 at the different SDQ questions are showed in Table 2. Differently from the prevalence of dysphagia as assessed through the SDQ, only 6 patients (3%) out of 177 were recorded as having dysphagia at the brainstem FS – dysphagia subscore with only one patient presenting brainstem FS – dysphagia subscore = 1 and 5 patients presenting brainstem FS – dysphagia subscore = 3. SDQ score was not associated with brainstem FS – dysphagia subscore ($P > 0.05$). Five out of the 6 patients classified as having dysphagia at the brainstem FS – dysphagia (score = 3) were also classified as having dysphagia at the SDQ questionnaire.

Clinico-demographic differences between patients with and without dysphagia are summarized in Table 3. Patients with dysphagia showed a higher prevalence of cognitive impairment (patients with dysphagia and cognitive impairment: 60% *vs* patients without dysphagia and cognitive impairment: 40%, $P = 0.01$), and a higher total MFIS score (12.6 ± 21.2 vs. 5.4 ± 3.2, $P = 0.02$) and physical MFIS score (13.6 ± 12.3 vs. 7 ± 8.3, $P = 0.04$).

At stepwise analysis, SDQ total score was associated only with BDI total score (coeff. 0.28, 95% CI: 0.10–0.46,

Table 1. Demographic and clinical features of patients with multiple sclerosis (MS).

Subjects, *N*	177
Sex	
Male, *N* (%)	60 (34)
Female, *N* (%)	117 (66)
Age, mean (SD) (years)	46.1 (11.1)
EDSS, median (range)	3 (1–7)
Visual FS, median (range)	0 (0–3)
Brainstem FS median (range)	1 (0–4)
Pyramidal FS, median (range)	2 (0–5)
Cerebellar FS, median (range)	1 (0–4)
Sensory FS, median (range)	1 (0–4)
Bowel/Bladder FS, median (range)	2 (0–4)
Disease duration, median (range) (years)	13 (0–34)
MS course	
Relapsing, *N* (%)	116 (65)
Progressive, *N* (%)	61 (35)
Ongoing DMT	
Naive, *N* (%)	1 (0.5)
Interferon, *N* (%)	3 (2)
Teriflunomide, *N* (%)	3 (2)
Dimethyl fumarate, *N* (%)	12 (7)
Cladribine, *N* (%)	52 (29)
Alemtuzumab, *N* (%)	1 (0.5)
Anti-CD20, *N* (%)	65 (37)
S1P modulators, *N* (%)	38 (21)
Natalizumab, *N* (%)	2 (1)
Smocking status	
Yes, *N* (%)	15 (8)
No, *N* (%)	162 (92)
SDMT corrected, mean (SD)[1]	43.2 (11.5)
CVLT corrected, mean (SD)[1]	40.4 (12.8)
BVMT corrected, mean (SD)[1]	46.1 (12.5)
Cognitive impairment[1]	
Yes, *N* (%)	83 (51)
No, *N* (%)	80 (49)
BDI-II, mean (SD)[2]	3.5 (7.8)
BAI, mean (SD)[2]	2.8 (9.1)
PSQI, mean (SD)[2]	1.5 (3.0)
MFIS total, mean (SD)[2]	9.7 (18.6)
MFIS physical, mean (SD)[2]	11.2 (11.3)
MFIS cognitive, mean (SD)[2]	8.7 (10.6)
MFIS psychosocial, mean (SD)[2]	1.5 (2.1)

EDSS, Expanded Disability Status Scale; SD, standard deviation; MS, multiple sclerosis; FS, functional system; CFS, cerebral functional score; N, number; DMT, disease-modifying treatment; S1P, sphingosine 1-phosphate; SDMT, Symbol Digit Modality Test; CVLT, California Verbal Learning Test; BVMT, Brief Visuo-spatial Memory Test; BDI-II, Beck Depression Inventory; BAI, Beck Anxiety Inventory; PSQI=Pittsburgh Sleep Quality Index MFIS, Modified Fatigue Impact Scale.
[1]Data available for 163 patients; Cognitive impairment defined as CFS > 0.
[2]Data available for 148 patients.

$P = 0.004$) and PSQI total score (coeff. 0.46, 95% CI: 0.10–0.83, $P = 0.001$).

SDQ-EDSS was higher than Native-EDSS in the overall population (3.5 [1 – 7] *vs* 3 [1 – 7], $P < 0.001$) as well as in patients with EDSS ≤ 4.0 (2.5 [1–5] vs. 2.5 [1–4], $P < 0.001$). Similarly, SDQ-brainstem FS was higher than native-brainstem FS in the overall population (1 [0–5] vs. 1 [0–4], $P < 0.001$) as well as in patients with EDSS ≤ 4.0 (1 [0–5] vs. 1 [0–2], $P < 0.001$). In detail, we found differences between native- and SDQ-EDSS in 25 patients (14%) in the overall sample and differences between native- and SDQ-EDSS in 25 out of 125 patients (20%) in the subgroup of subject with EDSS ≤ 4.0. Similarly, we recorded differences between native- and SDQ-brainstem FS in 48 patients (27%) in the overall population and differences between native- and SDQ-brainstem FS in 33 out of 125 patients (26%) in the subgroup of patients with EDSS ≤ 4.0.

No clinico-demographic factors were associated with the native- and SDQ-EDSS mismatch in the overall population whereas, in the subgroup of patients with native-EDSS ≤ 4.0, only native-EDSS was associated with mismatch (odds ratio = 1.98, 95% CI: 1.10–3.61, $P = 0.02$). Similarly, in patients with Native-EDSS ≤ 4.0 mismatch in the brainstem FS score was associated with native EDSS (odds ratio = 1.89, 95% CI: 1.10–3.25, $P = 0.02$).

Discussion

We assessed swallowing issues in MS patients through the SDQ in a real-world clinical setting. We observed a prevalence of dysphagia in 56% of patients with MS. SDQ-brainstem FS was higher than native-brainstem FS and SDQ-EDSS was higher than native-EDSS. Finally, we found that the SDQ score correlated with both the total BDI score and the total PSQI score.

A recent meta-analysis including 54 studies showed a 44.8% prevalence of dysphagia in patients with MS with a high heterogeneity among countries.[13] The large heterogeneity could be partly imputed to the different tools applied to assess dysphagia [i.e., Dysphagia in Multiple Sclerosis questionnaire (DYMUS), clinical evaluation, electromyography, Eating Attitude Test at 10-items (EAT-10), author constructed questionnaire, and Fibreoptic Endoscopic Evaluation of Swallowing (FEES)].[13] In addition, each questionnaire needs language translation and proper validation with proper methods before being applied. Accordingly, some of the prevalence figures presented in the meta-analysis were not derived from studies applying validated questionnaires.[14,15] Moreover, the SDQ is a screening tool for the assessment of dysphagia, the results of which may differ from those obtained through diagnostic tools such as endoscopy (e.g., FEES). Further studies employing endoscopic techniques, especially in those patients with lower SDQ scores would facilitate an accurate diagnosis of dysphagia. Overall, the prevalence

Table 2. SDQ questionnaire: number and percentages of total answers scoring.

Question	Percentage of answers between 1 and 3	Number of answers between 1 and 3	Number of answers: 0	Number of Answers: 1	Number of answers: 2	Number of answers: 3
6. Do you need to swallow chewed-up food several times before it goes down your throat?	28.81	51	126	35	10	6
5. Do you feel you have too much saliva in your mouth; do you drool or have difficulty swallowing your saliva?	27.68	49	128	38	9	2
2. Are there any food residues in your mouth, cheeks, under your tongue or stuck to your palate after swallowing?	26.55	47	130	29	16	2
9. While eating, do you feel as if a lump of food is stuck in your throat?	25.99	46	131	34	9	3
12. Do you experience a change in your voice, such as hoarseness or reduced intensity immediately after eating or drinking?	23.73	42	135	26	15	1
10. Do you cough while swallowing liquids?	23.16	41	136	28	7	6
13. Other than during meals, do you experience coughing or difficulty breathing as a result of saliva entering your windpipe?	22.60	40	137	28	9	3
7. Do you experience difficulty in swallowing solid food (i.e., do apples or crackers get stuck in your throat)?	21.47	38	139	26	8	4
1. Do you experience difficulty chewing solid food, like an apple, cookie or a cracker?	19.77	35	142	20	10	5
11. Do you cough while swallowing solid foods?	17.51	31	146	25	4	2
14. Do you experience difficulty in breathing during meals?	14.12	25	152	16	7	2
4. Does chewed-up food dribble from your mouth?	8.47	15	162	11	4	0
8. Do you experience difficulty in swallowing pureed food?	7.91	14	163	11	3	0
3. Does food or liquid come out of your nose when you eat or drink?	5.08	9	168	7	2	0

calculated from the meta-analysis was almost in line with our figure, notwithstanding the aforementioned limitations. In our study, prevalence was calculated in a mono-centric fashion, thus overcoming possible heterogeneity due to country differences, and we applied an Italian validated tool (i.e., the Italian SDQ version),[6] thus increasing results' reliability. In the validation study, the prevalence of dysphagia was calculated based on the water swallowing test and only those patients with a positive water swallowing test were classified as having low, moderate, or high risk of dysphagia.[6] Therefore, a proper comparison is not feasible. However, in a previous multi-centric Italian study using DYMUS questionnaire the prevalence of dysphagia was reported to be 31%.[16] It is noteworthy that some of the symptoms most frequently reported by patients in the 14-item SDQ are not part of the DYMUS, highlighting the need for a comprehensive and highly sensitive tool for assessing dysphagia in patients with MS. Further studies could help to compare the sensitivity of SDQ and DYMUS for the assessment of dysphagia.

We reported differences in the EDSS assessed as for clinical practice compared to the EDSS enriched with the dysphagia assessment through the SDQ. The EDSS is a clinically meaningful scale to assess disability in MS but holds several limitations in clinical practice. It is known the high dependence of EDSS on ambulation and pyramidal FS. The burden of ambulation and pyramidal FS on the overall EDSS score reduce the weighting of subtle symptoms such as fatigue, cognition, behavioral issues, and dysphagia that may provide clues for undergoing disease progression. Regarding this limitation, Saccà et al

Table 3. Clinico-demographic features of patients without and with dysphagia.

	Patients without dysphagia	Patients with dysphagia	*P* value
Subjects, *N* (%)	78 (44)	99 (56)	
Sex			
Male, *N* (%)	34 (44)	26 (26)	0.01*
Female, *N* (%)	44 (56)	73 (74)	
Age, mean (SD) (years)	45.9 (11.6)	46.2 (10.8)	0.90
EDSS, median (range)	2.5 (1.5–7)	3 (1–7)	0.16
Disease duration, median (range) (years)	13 (0–33)	12 (0–34)	0.67
MS course			
Relapsing, *N* (%)	54 (69)	62 (63)	0.36
Progressive, *N* (%)	24 (31)	37 (37)	
Smocking status			
Yes, *N* (%)	9 (11)	6 (6)	0.29
No, *N* (%)	69 (89)	93 (94)	
SDMT corrected, mean (SD)[1]	44.5 (10.6)	42.2 (12.1)	0.22
CVLT corrected, mean (SD)[1]	41.3 (11.9)	39.7 (13.5)	0.45
BVMT corrected, mean (SD)[1]	48.5 (11.3)	44.2 (13.1)	0.03*
Cognitive impairment[1]			
Yes, *N* (%)	37 (40)	55 (60)	0.01*
No, *N* (%)	43 (60)	37 (40)	
BDI-II, mean (SD)[2]	2.2 (6.3)	4.4 (8.6)	0.09
BAI, mean (SD)[2]	1.7 (0.8)	3.5 (1.1)	0.27
PSQI, mean (SD)[2]	1.0 (0.2)	1.9 (0.4)	0.06
MFIS total, mean (SD)[2]	5.4 (13.2)	12.6 (21.2)	0.02*
MFIS physical, mean (SD)[2]	7 (8.3)	13.6 (12.3)	0.04*
MFIS cognitive, mean (SD)[2]	5.4 (13.2)	12.6 (21.2)	0.07
MFIS psychosocial, mean (SD)[2]	1.2 (1.8)	1.7 (2.3)	0.39

EDSS, Expanded Disability Status Scale; SD, standard deviation; MS, multiple sclerosis; N, number; SDMT, Symbol Digit Modality Test; CVLT, California Verbal Learning Test; BVMT, Brief Visuo-Spatial Memory Test; BDI-II, Beck Depression Inventory; MFIS, Modified Fatigue Impact Scale.

[1] Data available for 163 patients.

[2] Data available for 148 patients.

* Using unpaired two-tailed *t*-test, chi-square or Wilcoxon rank-sum test as appropriate; $P < 0.05$.

demonstrated that EDSS not including cognitive assessment in clinical practice underestimates the disability in MS patients, being lower than the EDSS corrected for the CFS.[17] Similarly, the use of the SDQ in clinical practice for the assessment of dysphagia resulted in a higher brainstem FS, leading to an increase in the final EDSS score, especially in patients without ambulation issues. Therefore, although dysphagia is included in the EDSS, specifically in its brainstem FS subscore, it is usually underestimated in clinical practice, probably due to limited examination time and the lack of rapid assessment tools. Actually, when clinicians include dysphagia in the EDSS assessment it is a moderate dysphagia (5 patients out of 6) meaning that patients possibly referred themselves the dysphagia as a disabling symptom. Also, the EDSS only includes a generic evaluation, based only on patients reporting of swallowing difficulties (none–mild–moderate – marked). SDQ could be a quick and easy-to-use patient reported outcome to account for when patients complain of disease progression even in the absence of EDSS change.

We reported a correlation between dysphagia and cognitive impairment. Cognitive impairment is common in MS showing a prevalence between 34% and 65%.[18] Cognitive processing speed, memory, executive functions, and visuo-spatial processing are the most involved cognitive domains in MS.[18] The association between dysphagia and cognitive functions has been explored in other neurological disorders such as Parkinson's disease (PD)[19] and Alzheimer's disease (AD).[20] Impairment of learning, memory, and frontal executive functions has been associated with deficit of the oral phases of the swallowing process in PD,[19] thus suggesting the influence of cognitive function on the coordination of mastication and lingual motion needed for swallowing. In AD, altered attentional, emotional, and arousal conditions have been proposed as one of the mechanisms of dysphagia.[20] Further studies investigating the association between MRI alterations (i.e., brain atrophy and network disconnection) and dysphagia would be useful to find common pathophysiology mechanisms between cognitive and swallowing functions.

We observed a correlation between SDQ and depressive symptoms. The prevalence of depressive disorders is greater among individuals with MS compared to the general population.[21] Depressive symptoms usually exacerbate physical symptoms in MS.[22] Therefore, we may speculate that correlation between SDQ score and BDI score could be explained by an increased perception of disability related to MS. Previous published Italian studies did not assess the correlation between dysphagia and depressive symptoms. However, the association was already demonstrated in other studies.[23,24] In addition, swallowing relies on the interconnection between cortico-bulbar tract, arising from frontal lobe, and swallowing centers in the brainstem, that is, ventromedial reticular formation and the solitary tract nucleus.[25] Similarly, several papers have demonstrated that depression in MS is associated with lesions in the frontal lobe as well as in the cortico-bulbar tract fibres.[26–28] Therefore, we might speculate that depression and dysphagia might share similar pathological damages underpinning disability accrual.

Finally, in our study we demonstrated that dysphagia severity correlated with poorer sleep quality. Sleep

disorders (i.e., obstructive sleep apnea, insomnia, and restless legs syndrome) are common among patients with MS.[29] Poor sleep quality in MS may be in part explained by symptoms such as muscle spasms, periodic limb movements (PLM), nocturia, medication effects, and depression.[30] Poor sleep quality has previously been associated with greater disability, fatigue, depression, anxiety, pain, and dysphagia.[31,32] The association between sleep disorders and dysphagia might be explained by the disruption of anatomical pathways that regulate both sleeping and swallowing function. Ferini-Strambi et al demonstrated that patients with MS who suffered from PLM had greater magnetic resonance imaging (MRI) lesion loads localized in infra-tentorial regions, particularly in cerebellum and brainstem.[33] Similarly, infra-tentorial lesions have been associated with sleep-related breathing disorders (SRBD)[34] and REM sleep behavior disorder (RSBD).[35] Additionally, brainstem lesions may be associated with dysphagia,[25] further highlighting the role of these regions in both sleep and swallowing disturbances.

We found that dysphagia did not correlate with disease duration, and this result was in line with other similar studies.[5,6] As a matter of fact, dysphagia was detected also in patients with a short disease duration, suggesting that swallowing impairment could manifest since initial disease stages in MS. Furthermore, in contrast to other studies,[36,37] dysphagia did not relate to MS course and disability. This discrepancy could be partially explained by the different sizes and characteristics of the samples: our cohort included a relatively small number of progressive patients and numerous patients with mild forms of disease. Anyway, our intention was to verify the assessment of dysphagia in patients with mild clinical manifestation, emphasizing the importance of recognizing this symptom in its early stages in order to implement preventive measures.

We do acknowledge that this study is not without limitation. First, the cross-sectional nature of the study prevents us from drawing conclusion on the dynamic interplay among invisible symptoms and between invisible symptoms and overt physical disability. Second, the lack of MRI data hampers any speculations on the anatomic substrates of dysphagia in MS patients or with pathological changes associated with these symptoms (i.e., atrophy, brain lesion mapping, and network disconnection). Lastly, while we did apply the Italian validated SDQ to assess dysphagia, we could not rule out that SDQ only accounts for specific dysphagia symptoms underestimating the complex picture of swallowing problems. Other patient reported outcomes or, even better, other instrumental tests might be included in the analysis in order to be able to capture subtle signs related to dysphagia as well as to have objective tools avoiding subjective perception of the symptom.

Conclusions

Dysphagia is a common disabling symptom in patients with MS yet is underestimated in clinical settings due to EDSS-rater limitations. The SDQ is a quick, comprehensive and highly sensitive tool for assessing dysphagia in patients with MS and is easy-to-use in clinical practice. We found SDQ-assessed dysphagia in one MS patients out of two and demonstrated that proper dysphagia investigation could lead to an increase in the EDSS score, especially for fully ambulatory patients. SDQ could be possibly used as another proxy of progression, together with other available patient reported outcomes, when disability assessed through the EDSS does not show obvious changes.

Consent to Participate

All subjects gave written informed consent prior to study participation.

Author Contributions

Carotenuto Antonio, Roberta Lanzillo, Vincenzo Brescia Morra: Design and concept of the study; Carotenuto Antonio, Davide Ranucci, Fabrizia Falco, Valerio Nicolella, Cristina Di Monaco, Laura Migliaccio, Federica Lamagna, Federica Caracciolo, Martina Eliano, Maria Petracca, Marcello Moccia, Rberta Lanzillo, Carotenuto Antonio, Vincenzo Brescia Morra: Data acquisition; Carotenuto Antonio, Davide Ranucci, Valerio Nicolella: Data Analysis; Carotenuto Antonio, Davide Ranucci, Fabrizia Falco, Valerio Nicolella, Cristina Di Monaco, Laura Migliaccio, Federica Lamagna, Federica Caracciolo, Martina Eliano, Maria Petracca, Marcello Moccia, Rberta Lanzillo, Carotenuto Antonio, Vincenzo Brescia Morra: Manuscript Drafting; Carotenuto Antonio, Davide Ranucci, Fabrizia Falco, Valerio Nicolella, Cristina Di Monaco, Laura Migliaccio, Federica Lamagna, Federica Caracciolo, Martina Eliano, Maria Petracca, Marcello Moccia, Rberta Lanzillo, Carotenuto Antonio, Vincenzo Brescia Morra: Manuscript revision.

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Conflict of Interest

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Data Availability Statement

The anonymized dataset used and analyzed during the current study is available from the corresponding author upon reasonable request.

References

1. Dobson R, Giovannoni G. Multiple sclerosis – a review. Eur J Neurol. 2019;26(1):27-40.
2. Kurtzke JF. Rating neurologic impairment in multiple sclerosis. Neurology. 1983;33(11):1444-1452.
3. Lakin L, Davis BE, Binns CC, Currie KM, Rensel MR. Comprehensive approach to management of multiple sclerosis: addressing invisible symptoms—a narrative review. Neurol Ther. 2021;10(1):75-98.
4. Fernandes AMF, Duprat AD, Eckley CA, Silva LD, Ferreira RB, Tilbery CP. Oropharyngeal dysphagia in patients with multiple sclerosis: do the disease classification scales reflect dysphagia severity? Braz J Otorhinolaryngol. 2013;79 (4):460-465.
5. Calcagno P, Ruoppolo G, Grasso MG, de Vincentiis M, Paolucci S. Dysphagia in multiple sclerosis - prevalence and prognostic factors. Acta Neurol Scand. 2002;105 (1):40-43.
6. Sparaco M, Maida E, Bile F, et al. Validation of the swallowing disturbance questionnaire in people with multiple sclerosis. Mult Scler Relat Disord. 2024;81:105142.
7. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-173.
8. Goretti B, Niccolai C, Hakiki B, et al. The brief international cognitive assessment for multiple sclerosis (BICAMS): normative values with gender, age and education corrections in the Italian population. BMC Neurol. 2014;14(1):171.
9. Sica C, Ghisi M. The Italian versions of the Beck anxiety inventory and the Beck depression inventory-II: psychometric properties and discriminant power. Leading-Edge Psychological Tests and Testing Research. Nova Science Publishers; 2007:27-50.
10. Piscitelli D, Brichetto G, Geri T, et al. Italian adaptation and psychometric validation of the Fatigue Impact Scale (FIS) and its modified versions in adults with multiple sclerosis: a Rasch analysis study. Disabil Rehabil. 2024;18:1-14.
11. Curcio G, Tempesta D, Scarlata S, et al. Validity of the Italian Version of the Pittsburgh Sleep Quality Index (PSQI). Neurol Sci. 2013;34(4):511-519.
12. Bergamaschi R, Crivelli P, Rezzani C, et al. The DYMUS questionnaire for the assessment of dysphagia in multiple sclerosis. J Neurol Sci. 2008;269(1–2):49-53.
13. Mirmosayyeb O, Ebrahimi N, Shekarian A, et al. Prevalence of dysphagia in patients with multiple sclerosis: a systematic review and meta-analysis. J Clin Neurosci. 2023;108:84-94.
14. Eraković JL, Radulović LB, Idrizović ZA, Roganović MB. Screening of dysphagia in relapsing-remitting multiple sclerosis patients in Montenegro. Neurosciences. 2021;26 (4):331-338.
15. Sadeghi Z, Afshar M, Ebadi A, et al. Swallowing disorder in multiple sclerosis: modified version of the screening tool. J Rehabil. 2020;21(2):236-255.
16. Solaro C, Rezzani C, Trabucco E, et al. Prevalence of patient-reported dysphagia in multiple sclerosis patients: an Italian multicenter study (using the DYMUS questionnaire). J Neurol Sci. 2013;331(1–2):94-97.
17. Saccà F, Costabile T, Carotenuto A, et al. The EDSS integration with the Brief International Cognitive Assessment for multiple sclerosis and orientation tests. Mult Scler. 2017;23(9):1289-1296.
18. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. Lancet Neurol. 2020;19(10):860-871.
19. Kim JS, Youn J, Suh MK, et al. Cognitive and motor aspects of Parkinson's disease associated with dysphagia. Can J Neurol Sci. 2015;42(6):395-400.
20. Seçil Y, Arıcı Ş, İncesu TK, Gürgör N, Beckmann Y, Ertekin C. Dysphagia in Alzheimer's disease. Neurophysiol Clin. 2016;46(3):171-178.
21. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. Nat Rev Neurol. 2014;10(9):507-517.
22. Moore P, Hirst C, Harding KE, Clarkson H, Pickersgill TP, Robertson NP. Multiple sclerosis relapses and depression. J Psychosom Res. 2012;73(4):272-276.
23. Doruk C, Mocchetti V, Rives H, Christos P, Rameau A. Correlations between anxiety and/or depression diagnoses and dysphagia severity. Laryngoscope. 2024;134 (5):2115-2120.
24. Sadeghi Z, Ghoreishi ZS, Flowers H, Mohammadkhani P, Ashtari F, Noroozi M. Depression, anxiety, and stress relative to swallowing impairment in persons with multiple sclerosis. Dysphagia. 2021;36(5):902-909.
25. Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. Physiol Rev. 2001;81 (2):929-969.
26. Gobbi C, Rocca M, Riccitelli G, et al. Influence of the topography of brain damage on depression and fatigue in

patients with multiple sclerosis. Mult Scler. 2014;20 (2):192-201.
27. Pujol J, Bello J, Deus J, Martí-Vilalta JL, Capdevila A. Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. Neurology. 1997;49 (4):1105-1110.
28. Baller EB, Sweeney EM, Cieslak M, et al. Mapping the relationship of white matter lesions to depression in multiple sclerosis. Biol Psychiatry. 2024;95(12):1072-1080.
29. Braley TJ, Boudreau EA. Sleep disorders in multiple sclerosis. Curr Neurol Neurosci Rep. 2016;16(5):50.
30. Fleming WE, Pollak CP. Sleep disorders in multiple sclerosis. Semin Neurol. 2005;25(1):64-68.
31. Vitkova M, Gdovinova Z, Rosenberger J, et al. Is poor sleep quality associated with greater disability in patients with multiple sclerosis? Behav Sleep Med. 2018;16 (2):106-116.
32. Hamidi M, Rezaei A, Rezaeimanesh N, Sahraian MA, Moghadasi AN. Dysphagia in relation with depression, anxiety, fatigue, sleep quality, and pain in multiple sclerosis. Mult Scler Relat Disord. 2023;80:105184.
33. Ferini-Strambi L, Filippi M, Martinelli V, et al. Nocturnal sleep study in multiple sclerosis: correlations with clinical and brain magnetic resonance imaging findings. J Neurol Sci. 1994;125(2):194-197.
34. Braley TJ, Segal BM, Chervin RD. Sleep-disordered breathing in multiple sclerosis. Neurology. 2012;79 (9):929-936.
35. Tippmann-Peikert M, Boeve BF, Keegan BM. REM sleep behavior disorder initiated by acute brainstem multiple sclerosis. Neurology. 2006;66(8):1277-1279.
36. Abraham S, Scheinberg LC, Smith CR, LaRocca NG. Neurologic impairment and disability status in outpatients with multiple sclerosis reporting dysphagia symptomatology. Neurorehabil Neural Repair. 1997;11(1):7-13.
37. De Pauw A, Dejaeger E, D'Hooghe B, Carton H. Dysphagia in multiple sclerosis. Clin Neurol Neurosurg. 2002;104(4):345-351.

