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ORIGINAL ARTICLE

Study of Nonmotor Manifestations in a Sample of Egyptian Multiple Sclerosis Patients

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Abstract

Background: **Nonmotor symptoms are commonly reported with multiple sclerosis (MS) patients including fatigue, depression, anxiety, pain, cognitive impairment, sleep disorders, pseudobulbar affect, sexual dysfunction, paroxysmal symptoms, and bladder and bowel control problems. However, such manifestations are not sufficiently reported in Egypt.**

Aim: **This study aimed to estimate the proportion of nonmotor symptoms associated with MS amongst Egyptian patients and investigate their relationship with MS course and the related disability.**

Method: **A cross-sectional study was conducted on 120 MS patients with different clinical courses in Al-Azhar University hospitals from January 2020 to January 2021. All patients diagnosed with MS using MRI and able to give the required answers were recruited. All patients were assessed for the nonmotor symptoms using reliable instruments.**

Results: **A total 119 MS patients were analyzed including 78 relapsing remitting MS and 41 secondary progressive MS. Females represented 63.9% of the studied patients. Fatigue affected 62.2%, depression affected 78.2%, anxiety affected 39.5%, cognitive impairment affected 42%, sleep disorders affected 81.5%, pain affected 59.7%, pseudobulbar affected 6.7%, sexual dysfunction affected 23.4%, and paroxysmal symptoms affected 6.8% of the MS patients. Additionally, bladder and bowel control scales showed mean ± standard deviation (SD) of 14 ± 6.6 and 14.9 ± 7.6, respectively. On the other hand, significant associations were found between the nonmotor symptoms and each of MS course and expanded disability status scale.**

Conclusion: **Nonmotor symptoms are common in Egyptian patients with MS, and proximal to that previously reported. As these symptoms are clearly related to neural pathways affection, they are associated with progressive form of MS and high expanded disability status scale.**

Keywords: Expanded disability status scale, Multiple sclerosis, Non-motor

1. Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system characterized by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring.[1] Theprevalence of MS in Egypt varied according to reports and year of estimation which ranged from 0.5 to 3.7%.[2] A clinical presentation suggesting focal demyelination of the central nervous system should concern MS diagnosis.[3] Magnetic resonance imaging (MRI) is the gold standard tool to diagnose MS with sensitivity and specificity of up to 87 and 73%, respectively, using MRI-based McDonald criteria.[4] Relapsing-remitting MS (RRMS) is the most common type of MS at onset of the disease which is characterized by clearly defined attacks with partial or complete recovery.[5]

Primary progressive MS (PPMS) is characterized by progressive disability from disease onset with occasional stationary, short-time small improvements, or acute relapses.[6] Secondary progressive MS (SPMS) is characterized by an initial RRMS disease course followed by gradual worsening.[7]

Some MS symptoms are grouped and entitled 'nonmotor symptoms' including cognitive

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impairment, depression, anxiety, lower urinary tract dysfunction, pain, fatigue, and others.[8] Individually, paroxysmal symptoms including paroxysmal diplopia, facial paresthesia, trigeminal neuralgia, ataxia, and dysarthria are characterized by brief events occurring frequently that are triggered by movement or sensory stimuli.[9] Additionally, Sexual dysfunction is a very common nonmotor symptom affecting up to 50% of MS who become completely inactive, and 20% become less active.[10] Moreover, fatigue is the most common symptom among MS patients which was reported up to 86%.[11] The fatigue associated with MS is described as physical exhaustion that is not correlated to the amount of activity performed.[12] Sleep disorders is also common as a result of restless legs syndrome, obstructive sleep apnea, periodic limb movements of sleep, rapid eye movement sleep behavior disorder, and narcolepsy.[13] Depression affects up to two-thirds of patients with MS as some comorbidities contribute to depression in MS such as pain, anxiety, fatigue, substance abuse, and cognitive impairment.[14] Pain is also very common symptom in patients with MS including headache, neuropathic extremity pain, back pain, Lhermitte sign, painful spasms, and trigeminal neuralgia.[15] Cognition is also common symptom.[16] The prevalence and pattern of the non-motor symptoms, and their relation to MS-related disability and MS clinical course among Egyptian MS patients have not been studied. Therefore, this study aimed to estimate proportion of each nonmotor symptom and investigate potential relationship to EDSS scale, disease clinical course, and other clinical variables.

2. Method

2.1. Study design

A cross-sectional study was carried out at Al-Azhar University Hospitals during the period from January 2020 to January 2021. The Ethical Committee of the Faculty of Medicine, Al-Azhar University approved the study protocol, and written informed consent was obtained from all patients before starting the study.

2.2. Patients

It was planned to recruit a total 100 patients with MS as consecutive sample including all candidates who were admitted to the hospital from the start of the study until fulfilling the required sample size. The sample size calculation was based on the following consumptions: the prevalence of non-motor symptoms is 50%, type I error is 5%, and the accepted difference is up to 5% of the true population. The required sample size was increased to be 119 MS patients, assuming 20% incomplete data. The inclusion criteria included adult patients with age greater than or equal to 20 years and MRI confirmed diagnosis with MS with any degree of severity, and no exclusion criteria.

2.3. Assessments

Patients fulfilled the inclusion criteria were assessed clinically using physical examination and expanded disability status scale (EDSS).[17] Detailed history regarding MS disease and nonmotor symptoms was taken. The nonmotor symptoms include fatigue which was assessed using Fatigue Rating Scale,[18] neuropsychiatric symptoms that were evaluated according to DSM-V,[19] depression that was assessed using the Beck Depression Inventory,[20] anxiety which was assessed using Hospital Anxiety and Depression Scale,[21] pseudobulbar affect that was assessed using Center for Neurologic Study-Liability Scale (CNS-LS),[22] cognitive impairment that was evaluated using symbol digit modalities test,[23] pain that was assessed using Brief Pain Inventory,[24] paroxysmal symptoms that were asked for, sleep disorders that were assessed using the Epworth Sleepiness Scale, bladder dysfunction which was assessed using Bladder Control Scale (BLCS),[25] bowel dysfunction which was assessed using Bowel Control Scale,[26] sexual dysfunction that was evaluated using Intimacy and Sexuality Questionnaire-19.[27]

2.4. Statistical method

Qualitative data were presented as frequencies and percentages, and tested among the groups using χ^2 or Fisher exact test, as an appropriate. Quantitative data were expressed as mean ± standard deviation (SD), and tested among the groups using independent samples *t*-test or one-way ANOVA test according to number of values of independent variable. Correlation tests were conducted using Pearson correlation coefficient (r) with the following interpretation criteria: 1–0.8; excellent, 0.79–0.6; strong, 0.59–0.4; moderate, 0.39–0.2; weak, and 0.19–0; very weak. All tests were carried out at 0.05 level of significance using IBM SPSS v.26 software for required analysis.

3. Results

3.1. Patients

A total MS patients of 119 were recruited including 43 males and 76 females, aged

31.92 ± 8.719 years, and had BMI of 24.81 ± 2.402. Among them, 70 patients were married and 59 and 35 patients got high school and university, respectively. The clinical course of the MS was RRMS in 78 patients and SPMS in 41 patients. The disease duration was less than 3 years in 42 patients, 3–10 years in 49 patients, and more than 10 years in 28 patients. Number of lesions detected by MRI was less than 3 lesions in 15 patients, 3–10 lesions in 65 patients, and more than 10 lesions in 39 patients. Spine MRI yielded lesions in 58 patients, while the remaining patients (61 patients) showed negative results.

3.2. Non-motor symptoms

Depression was the most frequent nonmotor symptom reported among the studied patients as 93 experienced variable degrees of depression as shown in (Table 1). Sleep abnormalities were also common either unlikely or excess, where 97 patients suffered from sleep disturbances. Additionally, 71 patients suffered from mild, moderate, or severe pain among 119 MS patients. Furthermore, fatigue was high prevalent as 74 patients gave fatigue history. Cognitive impairment was observed in 50 MS patients. Sexual dysfunction was reported in only 29 patients with different degrees as shown in (Table 1). Moreover, paroxysmal symptoms were obtained from 20 patients with different presentations as shown in (Table 1). On the other hand, bladder control scale and bowel control scale exhibited mean ± SD of 14 ± 6.6 and 14.9 ± 7.6, respectively.

3.3. Non-motor symptoms in relation to MS

Fatigue was more frequent among SPMS patients compared with RRMS patients (100 vs. 42.3%). Additionally, all SPMS patients (100%) had depression compared with 66.7% of RRMS patients. Pseudobulbar affect and cognitive impairment were higher in frequencies among SPMS patients than those among RRMS patients as shown in Table 2. Moreover, all SPMS patients experienced pain with different severity (100%) compared with 38.5% of RRMS patients. Also, 38 SPMS patients complained sleep disorder compared with 57 RRMS patients including excessive and average sleep as shown in Table 2. Sexual dysfunction and paroxysmal symptoms were more frequent among SPMS patients relative to RRMS patients (Table 2). On the other hand bladder and bowel control scales showed higher mean scale in SPMS group compared with RRMS group as shown in Table 2 ($P < 0.001$).

Table 1. Nonmotor symptoms occurrence among the studied patients.

Variable	Number ($n = 119$) (%)
Fatigue	
Negative	45 (37.8)
Positive	74 (62.2)
Depression	
Mild	47 (39.5)
Moderate	31 (26.1)
No	26 (21.8)
Severe	15 (12.6)
Anxiety	
Abnormal	25 (21.0)
Borderline	22 (18.5)
Normal	72 (60.5)
Pseudobulbar effect	
Negative	111 (93.3)
Positive	8 (6.7)
Cognitive impairment	
Abnormal	50 (42.0)
Normal	69 (58.0)
Severity of pain	
Mild	32 (26.9)
Moderate	31 (26.1)
Negative	48 (40.3)
Severe	8 (6.7)
Sleep	
Average	35 (29.4)
Excessive	62 (52.1)
Unlikely	22 (18.5)
Sexual	
Negative	90 (75.6)
Primary	1 (0.8)
Secondary	16 (13.4)
Tertiary	12 (10.1)
Paroxysmal symptoms	
Negative	99 (83.2)
Present dysphasia	5 (4.2)
Present hemifacial spasm	5 (4.2)
Present Lhermitte's Sign	1 (0.8)
Present trigeminal neuralgia	9 (7.6)
Bladder control scale, mean ± SD	14.00 (6.574)
Bowel control scale, mean ± SD	14.87 (7.601)

3.4. Non-motor symptoms in relation to EDSS score

As shown in Table 3, higher mean EDSS was shown among MS patients with fatigue compared with those with negative fatigue ($P < 0.001$). Additionally, MS patients with severe pain, borderline anxiety, pseudobulbar affect, cognitive impairment, severe pain, excessive sleep disorder, primary/secondary sexual dysfunction, or Lhermitte's Sign showed higher mean EDSS scores compared with other MS patients. On the other hand, the correlations between EDSS and each of bladder control scale and bowel control scale were significant with a positive strong to excellent correlation coefficients (Table 3).

Table 2. Relationship between nonmotor symptoms and expanded disability status scale.

Nonmotor symptoms	Expanded disability status scale		*P*-value
	Mean	SD	
Fatigue			
Negative	2.500	0.4885	<0.001*
Positive	4.345	1.4116	
Depression			
Mild	2.851	0.9320	<0.001*
Moderate	4.661	1.0908	
No	2.577	0.4169	
Severe	5.900	0.5071	
Anxiety			
Abnormal	2.800	1.0104	<0.001*
Borderline	4.864	1.4734	
Normal	3.569	1.3539	
Pseudobulbar effect			
Negative	3.468	1.3370	<0.001*
Positive	6.125	0.5175	
Cognitive impairment			
Abnormal	4.940	1.1765	<0.001*
Normal	2.710	0.7593	
Severity of pain			
Mild	3.250	1.1846	<0.001*
Moderate	5.161	0.9865	
Negative	2.604	0.5739	
Severe	5.625	0.6944	
Sleep disorder			
Average	3.443	1.3491	0.017
Excessive	3.984	1.5122	
Unlikely	3.023	1.2486	
Bladder control scale, Pearson correlation coefficient	0.796	<0.001	
Bowel control scale, Pearson correlation coefficient	0.817	<0.001	
Sexual			
Negative	3.328	1.2790	<0.001*
Primary	6.000	.	
Secondary	5.438	0.9106	
Tertiary	3.458	1.5588	
Paroxysmal symptoms			
Negative	3.949	1.4097	<0.001*
Present dysphasia	2.300	0.2739	
Present hemifacial spasm	2.000	0.0000	
Present Lhermitte's Sign	3.500	.	
Present trigeminal neuralgia	2.000	0.0000	

The above comparisons were conducted using *t*-test (2 levels) or one way-ANOVA test (>2 levels) according to levels.
* Significance *P* value <0.001.

4. Discussion

To our knowledge, it is the first study to address the question of how pattern is the non-motor symptoms associated with MS in Egyptian patients and how are they correlated with the disease severity and clinical course. Fatigue is one of these nonmotor symptoms showing a percentage of 62.2% among Egyptian MS patients of the present study. Globally, the most frequent non-motor symptom alleged by MS patients is fatigue affecting between 50% and 80% of the patients.[28] We found that fatigue was more frequent in SPMS compared with RRMS. Consistently, a large prospective longitudinal study reported that fatigue was lower in RRMS patients than in other MS subtypes including SPMS.[29] The physiopathology of fatigue may be explained by dysfunction of circuits including thalamus, basal ganglia, and frontal cortex affecting by the CNS lesions or the products of inflammation.[30]

The second nonmotor symptom reported in the present study was depression. Generally, we found that depression affected 78.2% of the studied MS patients and it was associated with SPMS and high EDSS score. Specifically, moderate-to-severe depression was reported in 38.7% subjects. In comparison with the present findings, variable prevalence of MS-associated depression has been reported in the literature. In agreement with our findings, the annual prevalence rate of depression

Table 3. Relationship between nonmotor symptoms and Multiple sclerosis course.

Nonmotor symptoms	Multiple sclerosis type		*P*-value
	Relapsing-remitting multiple sclerosis ($n = 78$)	Secondary progressive multiple sclerosis ($n = 41$)	
Fatigue			
Negative	45	0	<0.001*
Positive	33	41	
Depression			
Mild	43	4	<0.001*
Moderate	9	22	
No	26	0	
Severe	0	15	
Anxiety			
Abnormal	22	3	<0.001*
Borderline	5	17	
Normal	51	21	
Pseudobulbar effect			
Negative	78	33	<0.001*
Positive	0	8	
Cognitive impairment			
Abnormal	12	38	<0.001*
Normal	66	3	
Severity of pain			
Mild	26	6	<0.001*
Moderate	4	27	
Negative	48	0	
Severe	0	8	
Sleep disorder			
Average	26	9	0.008*
Excessive	33	29	
Unlikely	19	3	
Bladder, mean ± SD	10.69 ± 5.65	20.29 ± 2.05	<0.001
Bowel, mean ± SD	10.31 ± 5.06	23.54 ± 1.87	<0.001
Sexual			
Negative	68	22	<0.001*
Primary	0	1	
Secondary	2	14	
Tertiary	8	4	
Paroxysmal symptoms			
Negative	58	41	<0.001*
Present dysphasia	5	0	
Present hemifacial spasm	5	0	
Present Lhermitte's Sign	1	0	
Present trigeminal neuralgia	9	0	

The above comparisons were conducted using *t*-test (bladder and bowel) or Fisher exact test/Chi-square test (other variables).
*Significant *P*-value at 0.05 level of significance.

was estimated in 2003 to be 26%,[31] and up to 36.3% in a recent study published in 2021.[32]

The third non-motor symptom reported in the present study was anxiety representing 39.5% of the study sample, which was associated with SPMS and lower EDSS score. Consistently, a very recent study published in 2022 reported a near prevalence which was 41.6%.

The fourth nonmotor symptom reported in the present study was pseudobulbar affect, which was reported in only 6.7% MS patients. Also, it was significantly associated with the progressive form of MS and the high score of EDSS. In agreement with the present findings, a very recent meta-analysis published in 2022 and built on 10 studies reported that the pooled prevalence of pseudobulbar affect ranged from 11 to 35% among MS patients with a high level of heterogeneity.[33]

The fifth nonmotor symptom reported in the present study was cognitive impairment. It affected 42% of the studied subjects and was significantly associated with SPMS and EDSS score. Consistently, a prevalence of 40–65% of cognitive impairment has been reported in MS patients.[34,35]

Pain as a nonmotor symptom affected all the studied MS patients in our study with different

degrees of severity. Similar and lower proportions have been reported in the literature. Up to 75% of MS experienced pain as a primary because of the disease course or secondary to fatigue and spasticity.[36] In a meta-analysis, the estimated pooled prevalence of pain in MS was 63% (95% CI: 55–70%). Several types of pain are reported including neuropathic extremity pain, trigeminal neuralgia, Lhermitte's sign, headache, painful spasms, and back pain.[37]

Sleep disorder is another non-motor symptom reported in the present study in 81.5% of MS subjects. Moreover, higher severe sleep disorder was associated with the clinical course of MS and the EDSS score. In agreement with our findings, up to 60% sleep disorders have been reported.[13]

Sexual dysfunction was also reported in the present study that affects 24.4% of the studied patients, and was associated with MS type and EDSS score. However, different studies reported a higher prevalence of sexual dysfunction in MS of 40–80% in women and 50–90% in men Bladder and bowel control scales used in the present study showed some affections that were associated with MS clinical course, and correlated with ESDD score. These findings are in consistence with previously published studies.[38,39] Correlation between bladder dysfunction and EDSS score was also demonstrated in a study assessing the productivity of EDSS in the bladder dysfunction.[40] Also, bowel dysfunction exhibited an association with high EDSS and the disease course,[41] which agreed with the present results. The pathophysiology of such control problems is demyelination of neural pathways that control the bladder and bowel.[42]

4.1. Limitations

Community constraints regarding sexual dysfunction assessment, especially women, were managed by keeping the interview more confidential and offering a sexually-matched interview assistants. Recall bias was also a risk in gathering historical data. It was minimized by asking relatives to ensure all data accuracy, and by excluding those who could not give sufficient data.

4.2. Conclusion

Nonmotor symptoms occurrence among MS Egyptian patients is nearly similar to that reported globally. Additionally, the nonmotor symptoms are associated with the disease clinical course and the EDSS of MS. The study suggest to validate the EDSS to early predict the nonmotor symptoms in a longitudinal study.

Conflicts of interest

There are no conflicts of interest.

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