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Predictors of Long-term Disability in Multiple Sclerosis: Real World Data from a Cohort of Egyptian Patients

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Abstract

Background: Specification of prognostic factors in multiple sclerosis (MS) is crucial for clinicians to guide therapeutic protocols. This study aimed to identify demographic, clinical, and radiological factors associated with disability on a long-term basis in relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS).

Methods: This was a retrospective study conducted on patients with RRMS and SPMS with a disease duration of at least 10 years. Demographic, clinical, and radiological parameters were collected from the medical records.

Results: During the study period, 217 patients were recruited with a mean disease duration of 14.9±4.6 (range: 10-35) years. Regression analysis revealed that age (B=0.071, CI: 0.00-0.132, *P*=0.025), male sex (B=–0.825, CI: –1.444 to –0.206, *P*=0.009), duration between first 2 attacks (B=-0.007, CI: -0.015-0.000, *P*=0.037), and involvement of pyramidal (B=0.754, CI: 0.051-1.457, *P*=0.036) or cerebellar domains (B=1.355, CI: 0.542-2.168, *P*=0.001) at disease onset were the only parameters that had an independent effect on EDSS.

Conclusion: Predictors of long-term disability in our cohort were closely similar, but not typically identical to predictors reported in the literature. Age, male sex, short duration between first 2 relapses pyramidal and cerebellar affection were the strongest predictors of disability in patients with RRMS and SPMS.

Keywords: EDSS; Early predictor; Long-term prognosis; Multiple sclerosis

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Introduction

Early and reliable prediction multiple sclerosis (MS) and the disease course are major determinants for tailoring disease-modifying therapy (DMT) for individual patients with relapsing-remitting MS (RRMS).[1,2] Due to the multiplicity of pathological mechanisms, patients with MS acquire a highly variable disease course.[3,4] At early disease course, several predictors can help clinicians identify patients at risk for rapid progression or aggressive disease course[4] and, hence, provide more efficacious DMTs without risking the patients' safety.

In the literature, several demographic, clinical, and radiological parameters have been reported to predict long-term disability progression.[4-6] However, the data were not consistent among different populations and countries. For instance, in a cohort of Chinese patients, the strongest predictors of long-term progression were age at onset, degree of recovery from the presenting attack, and number of relapses during the first 2 years after disease onset.[4] Meanwhile, data from a French population-based registry revealed a negative correlation between the duration of staying in the benign state and the final expanded disability status scale (EDSS) score at advanced age on long-term follow-up.[7]

In the Middle East region, data are scarce regarding predictors of long-term progression of MS. One of the largest studies conducted in this region was a retrospective study conducted in Egypt on 1581 patients during 2001-2015. The results of this study were significantly different from the data reported in Western countries, showing that the presence of infratentorial lesions was the only independent predictor in disease progression.[8] Accordingly, we aimed to identify potential early predictors of EDSS progression among a cohort of Egyptian patients with MS for at least 10 years.

Methods

Participants and Procedures

This was a retrospective observational study conducted on adult patients diagnosed with RRMS and secondary progressive MS (SPMS) registered at the MS unit of Alexandria University MS Clinic during 2014-2019. Inclusion criteria were as follows: Diagnosis of RRMS or SPMS according to the revised 2017 McDonald's

criteria,[9] having a disease onset of at least 10 years, and having a complete medical record without missing data. Patients with other types of MS and those with debatable diagnoses were excluded from this study.

Data Collection

Demographic, clinical, and radiological variables were collected from patients' medical records. Demographic variables included age and sex. Clinical factors included age at onset of MS, disease duration (in years), duration between the first two attacks, total number of relapses, type of presentation at disease onset (i.e., monosymptomatic versus polysymptomatic onset), symptom domains involved at disease onset (i.e., visual, brainstem, sensory, pyramidal, cerebellar, bowel/bladder, and/or spinal), family history of MS, family history of other immune-mediated diseases, duration before starting DMT, DMT administration (no/yes variable), and duration on DMT intake. Radiological variables included the presence of T1 blockholes and T2 periventricular, infratentorial, and spinal lesions on initial magnetic resonance imaging (MRI).

The EDSS is a validated well-known clinical scale designated to measure the degree of disability in MS.[10] It is divided into an ambulation score and seven functional system scores (FSS) i.e., visual FSS, brainstem FSS, pyramidal FSS, cerebellar FSS, sensory FSS, bowel/bladder FSS, and mental FSS.[10] The scale ranges from zero to 10 with zero denoting no disability and 10 denoting fatal disability because of MS.[10] The EDSS was performed in this study by certified raters through NeuroStatus.[11]

Statistics and Data Analysis

All data were fed to a computer and analyzed using IBM Statistical Package for the Social Sciences (SPSS) software, version 22.0. Qualitative variables were expressed as numbers and percentages. Quantitative data were expressed as mean or median, standard deviation, minimum, and maximum. The normal distribution of variables was verified using Kolmogorov-Smirnov test. Mann-Whitney test was used to compare means between the studied groups, and Spearman's coefficient was used to study the correlation between EDSS scores and quantitative variables. Linear regression analysis was used to detect the most independent factors affecting EDSS scores. $P < 0.05$ was considered as statistically significant

Results

Demographic and Clinical Characteristics

Of the 217 patients studied, 67.3% were women. The mean ± S D age of the patients was 38.8 ± 8.8 (16-63) years, and the mean ± SD age at onset was 24.2 ± 8.3 (12-48) years. The duration of MS ranged from 10 to 35 years with a mean ± SD of 14.9 ± 4.6 years. Of the 217 patients studied, 184 (84.3%) patients had a disease duration of 10 years and 33 (15.7%) had a disease duration of more than 10 years. EDSS scores ranged from 0 to 8, and the median score was 3.2 ± 2.4. Family history of MS was positive in 8.8% of the patients, and family history of other immune-mediated diseases was positive in 12.9%.

About 58.1% had a monosymptomatic presentation at disease onset, whereas polysymptomatic onset was seen in 41.9% of the patients. The domains involved at disease onset were sensory (40.6%), pyramidal (35.5%), visual (30.4%), cerebellar (18.9%), brainstem (16.6%), cerebral (6%), and bowel/bladder (2.8%), respectively. The mean duration between the first two attacks was 37.7 ± 42.2 months, and the total number of relapses ranged from 2 to 45 with a mean of 5.1 ± 6.3 months.

The duration between initial presentation to starting DMT ranged from one to 34 years (mean ± SD = 12.5 ± 5.5 years). Of the 170 (78.3%) patients receiving DMT, the mean duration of treatment was 1.92 ± 2.32 years. Disease modifying therapies administered were intramuscular interferon β1a (7.8%), subcutaneous interferon β1a (19.8%), subcutaneous interferon β1b (24.4%), fingolimod (13.4%), natalizumab (0.5%), ocrelizumab (1.8%), rituximab (3.2%), azathioprine (2.3%), methotrexate (2.3%), cyclophosphamide (0.2%), and monthly methylprednisolone (2.3%).

Regarding initial MRI findings, all patients (100%) had T2 periventricular lesions. T2 infratentorial lesions, T2 spinal lesions, and T1 blackholes were seen in 52.1%, 39.2%, and 81.1% of the patients, respectively.

The Relation Between EDSS Scores and Different Studied Parameters

Tables 1 and 2 detail the relation between EDSS scores and the studied demographic, clinical, and radiological parameters among the studied groups. Men had higher EDSS scores (4 [range: 0-8]) than women (2.5 [range:0-9]) ($P = 0.018$). Patients with polysymptomatic presentation at disease onset had a higher EDSS median score (4 [range: 0-9]) compared patients with monosymptomatic onset ($P = 0.003$). Involvement of pyramidal ($P = 0.015$) and cerebellar domains ($P = 0.004$) at disease onset were significantly associated with worse EDSS scores.

On studying the correlation between EDSS and quantitative parameters (Table 2), older age and older age at onset of disease were weakly correlated with EDSS scores ($r = 0.257$, $P < 0.001$ and $r = 0.253$, $P < 0.001$, respectively). Longer duration between first 2 attacks was very weakly and inversely correlated with lower EDSS ($r = -0.151$, $P = 0.026$). The same was seen with total number of relapses ($r = -0.174$, $P = 0.010$).

Regression Analysis

Univariate analysis (Table 3) showed a significant effect of several parameters on EDSS scores such as patient's current age at time of recruitment, sex, age at onset of disease, polysymptomatic onset, involvement of pyramidal

Table 1. Relation Between EDSS and Different Qualitative Parameters (n = 217)

Parameters	No.	Median (Min.– Max.)	Mann-Whitney Test	*P* Value
Gender				
Male	71	4 (0–8)	4159.5*	0.018*
Female	146	2.5 (0–8)		
Family history immune-mediated diseases	28	3 (0–7)	2569.5	0.804
Family history of MS	19	4 (1–6.5)	1428.0	0.082
Receiving DMT?				
No	47	4.5 (0-8)	3286.0	0.062
Yes	170	2.8 (0-8)		
Early MS Disease Characteristics				
Presentation at onset				
Monosymptomatic	126	2 (0–7.5)	4377.5*	0.003*
Polysymptomatic	91	4 (0–8)		
Domains involved at disease onset				
Visual	66	2.5 (0–8)	4755.0	0.591
Sensory	88	3 (0–8)	5389.5	0.526
Pyramidal	77	4 (0–8)	4313.5*	0.015*
Cerebellar	41	4.5 (0–7.5)	2556.5*	0.004*
Brainstem	36	3.5 (0–7)	3029.0	0.504
Cerebral	13	2 (0–6.5)	999.5	0.135
Bowel/bladder	6	3.8 (0–6)	615.5	0.908
Initial MRI Findings				
T2 infratentorial				
Yes	113	3 (0–8)	5414.0	0.315
No	104	2.5 (0–7.5)		
T1 blackholes				
Yes	41	4 (0–7.5)	3047.5	0.120
No	176	2.5 (0–8)		
T2 spinal				
Yes	85	3.5 (0–8)	5086.0	0.244
No	132	2.5 (0–7.5)		

Abbreviations: MRI, magnetic resonance imaging; MS, multiple sclerosis; DMT, disease-modifying therapy.
* Statistically significant at $P \leq 0.05$,

Table 2. Correlation Between EDSS and Different Quantitative Parameters Among Patients' Groups

Parameter	r_s	*P* value
Age	0.257*	<0.001*
Age of onset	0.253*	<0.001*
Disease duration	0.065	0.342
Duration between first 2 attacks	-0.151*	0.026*
Total number relapse	-0.174*	0.010*
Duration prior to DMT intake	-0.040	0.561
Duration of DMT intake	-0.015	0.824

Abbreviations: DMT, disease modifying therapy; r_s, Spearman coefficient.
*Statistically significant at $P \leq 0.05$

or cerebellar domains at disease onset, duration between first two attacks, and receiving DMT. On multivariate regression, age, sex, duration between first 2 attacks, and involvement of pyramidal or cerebellar domains at disease onset showed a significant and independent effect on EDSS, whereas age at onset, polysymptomatic onset, and receiving DMTs did not seem to have an independent effect. There was a significant positive correlation between the EDSS and patient's age (B: 0.071, P = 0.025), male sex (B: -0.825, P = 0.009), shorter duration between the first two attacks (B = 0.007, P = 0.037), and involvement of pyramidal (B = 0.754, P = 0.036) and cerebellar domains (B = 1.355, P = 0.001). None of the initial MRI findings studied had an impact on EDSS scores in our cohort of patients.

Discussion

Predicting disease progression based on patient characteristics and clinical parameters is one of the most challenging tasks in MS. We aimed to identify early predictors of long-term EDSS progression in patients with MS with a disease duration of at least 10 years. Older age, male sex, shorter duration between first 2 attacks, and involvement of pyramidal and cerebellar domains were the main independent predictors of worse EDSS scores in our cohort.

The findings in this study were consistent with several reports in the literature. A systematic review of 27 studies reported that incomplete recovery from the presenting attack, a short duration to first relapse, as well as early accumulation of disability were the strongest predictors of poor long-term EDSS progression.[6] The authors also stated that motor or cerebellar symptoms at onset predicted a more severe MS course and this was consistent with our study findings.[6] In contrast to our findings, the review included bowel/bladder involvement at onset as one of the strongest determinants of disability progression, which is not the case in our study. Similarly, Bermel et al,[5] in their 15-year prospective multicenter trial of patients treated with interferon β, reported the predictors of poor prognosis were male sex, older age at disease onset, short inter-relapse interval, frequent early relapses, early involvement of pyramidal, cerebellar, and/or bowel/bladder domains at presentation, and progressive disease at onset. This is consistent with our results. Other predictors were reported by Sotiropoulos et al,[12] who studied 360 patients with MS, and found that younger age at disease onset, the use of DMTs, and longer bowel/bladder symptoms-free duration were predictors of better recovery during the initial three years of MS disease.

In disagreement with our results, Bergamaschi et al,[13] in 2004, stated that on multivariate analysis the higher the number of the functional domains involved at MS onset and the higher the number of early attacks, the higher

Table 3. Univariate and Multivariate Analysis for the Parameters Affecting EDSS (n=217)

	Univariate				Multivariate[a]			
	B	95% CI		*P* Value	B	95% CI		*P* Value
		LL	UL			LL	UL	
Gender	-0.786	-1.454	-0.119	0.021*	-0.825	-1.444	-0.206	**0.009***
Age	0.072	0.037	0.107	<0.001*	0.071	0.009	0.132	**0.025***
Age of onset	0.067	0.030	0.104	<0.001*	-0.006	-0.071	0.059	0.859
Disease duration	0.022	-0.046	0.090	0.525				
Total number relapse	-0.015	-0.065	0.036	0.568				
Family history of immune diseases	0.092	-0.854	1.038	0.848				
Family history of MS	0.946	-0.169	2.060	0.096				
Early disease characteristics								
Mono vs polysymptomatic onset	0.978	0.349	1.607	0.002*	0.228	-0.476	0.931	0.524
Duration between first 2 attacks	-0.009	-0.017	-0.002	0.016*	-0.007	-0.015	0.000	**0.037***
Visual domain at onset	-0.141	-0.830	0.548	0.688				
Sensory domain at onset	0.173	-0.472	0.818	0.598				
Pyramidal domain at onset	0.841	0.188	1.494	0.012*	0.754	0.051	1.457	**0.036***
Cerebellar domain at onset	1.185	0.391	1.979	0.004*	1.355	0.542	2.168	**0.001***
Brainstem domain at onset	0.246	-0.606	1.098	0.570				
Cerebral domain at onset	-1.009	-2.338	0.320	0.136				
Bowel/bladder domain at onset	-0.046	-1.980	1.887	0.962				
DMT administration variables								
DMT intake	-0.778	-1.540	-0.015	0.046*	-0.471	-1.182	0.240	0.193
Duration prior to DMT intake	-0.012	-0.070	0.046	0.682				
Duration of DMT intake	-0.034	-0.171	0.102	0.622				
Initial MRI characteristics								
T2 infratentorial	-0.317	-0.950	0.316	0.325				
T1 Black holes	-0.674	-1.479	0.131	0.100				
T2 Spinal	-0.434	-1.081	0.213	0.188				

Abbreviations: Beta, standardized coefficients; CI, confidence interval; DMT, disease modifying therapy; LL, lower limit; MS, multiple sclerosis; MRI, magnetic resonance imaging; UL, upper limit.
[a] All variables with $P<0.05$ was included in the multivariate analysis; * Statistically significant at $P\leq0.05$.

EDSS acquired on long-term follow-up. Closely similar results were also reported by Hojjati et al,[14] who studied 263 patients with definite diagnosis of MS in Iran, they stated that the mean EDSS scores in patients who had monosymptomatic disease onset were significantly lower than the patients who had a polysymptomatic disease onset. In our study, however, the multivariate regression model did not confirm this finding.

As for the total number of relapses, the data in literature are inconsistent about whether the total number of relapses had an independent effect on long-term disease disability or not. Some studies were in line with our results that the total number of relapses does not necessarily affect long-term EDSS e.g., Rolak et al,[15] who prospectively evaluated 891 patients with RRMS for up to 21 years, and reported that there was no link between the degree of disability and the frequency of relapses. In contrast, Bsteh et al[16] observed 793 patients with a disease duration of 10 years and more and noted a positive significant correlation between the frequency of relapses and level of disability.

The use and the duration of DMT use were not found to have an independent effect on long-term EDSS which is contrary to most of the literature statements. Use of DMTs has consistently been reported to have a favorable effect on EDSS progression.[17-20] The contrasting findings in our study might be attributed to several factors i.e., the long duration before initiating DMTs (mean 12.5 years), a short treatment duration (men 1.95 years), as well as missing data about patients' compliance. Prior to 2014, most of the DMTs were not available in Egypt, and the few available DMTs were expensive and not imbursed. Therefore, drug compliance could not be guaranteed. Though our findings concerning the use of DMTs were odd, they match with what was reported by Claflin et al,[17] in their meta-analysis, that at least four years of DMT use is required to improve the EDSS. Similar data were reported by Chalmer et al,[21] who followed up 3795

patients from the Danish registry for a mean of 7 years, and noted that the later the initiation of DMTs, the shorter the time to an EDSS score of 6 and the shorter the time to death. Their data also support our findings that the non-significance of DMTs use might be attributed to their delayed initiation.

The presence of spinal lesions and/or infratentorial lesions at initial MRIs was not found to be an independent factor that affect long-term EDSS. This also is different from several literature studies. Infratentorial and spinal lesions at disease onset, even if asymptomatic, were linked to worse EDSS progression over the first 5 to 7 years of the disease,[22-25] this was contrary to our study. This was also different from the retrospective study conducted in Egypt on 1581 MS patients with a disease duration ranging from 1 to 257 months where the infratentorial lesions had an independent risk (odds ratio: 6, 95% CI: 2.99–12.02, P = 0.0005) for disease progression.[8] The difference noted in our study might be related to the different sample characteristics, longer disease duration, and different prevalence of infratentorial lesions. Several other MRI parameters were reported to predict long-term disability progression such as T2 burden,[26] brain volume,[27,28] and atrophy rates,[27,28] but these variables were not available in the medical records of our cohort of patients. In the study conducted by Hamdy et al,[8] in Egypt, black holes (odds ratio: 4.14, 95% CI: 3.08–5.58) and infratentorial lesions (odds ratio: 4.07, 95% CI: 3.21–4.99) on initial MRI had only an effect on progression on univariate analysis. On multivariate analysis, however, the infratentorial lesions had the only independent effect (odds ratio: 6, 95% CI: 2.99–12.02, P = 0.0005) as aforementioned.[8]

The main limitations of or study were the retrospective design, missing data about DMTs compliance, MRI T2 lesion load in the brain, and other potential radiological predictors of long-term disability progression. Thus, our study was mainly directed to clinical and demographic predictors of long-term disability progression.

Conclusion

Predictors of long-term disability in our cohort were closely similar, but not typically identical, to predictors reported in the literature. Age, male gender, short duration between first 2 relapses pyramidal and cerebellar affection were the strongest predictors of disability in patients with RRMS and SPMS.

Conflict of Interest Disclosures

None to declare.

Ethical Statement

We obtained an ethical approval to conduct this research from the Ethics Committee of the faculty of medicine at Alexandria University (IRB NO: 00012098, FWA NO: 00018699) prior to conducting this research. Informed consents were obtained from the patients to use their anonymous data for research purposes.

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