

## Original Article **Disability status among multiple sclerosis patients in relation to clinical features and switched drugs**

Neurology

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### ABSTRACT

**Background:** Multiple sclerosis (MS) is a progressive neurodegenerative disease that causes irreversible disability. The main cause of switching between disease modifying therapies (DMTs) in MS is the suboptimal response in which relapses and disability progression are the main clinical outcome measures.

**Objective:** This study aims to identify the baseline clinical features of disability among MS patients who underwent switching between two or more DMTs.

**Methodology:** This is a cross-sectional study based on records of MS patients who had been actively receiving available DMTs at the MS unit of Nasser Institute Hospital for Research and Treatment. The data was reviewed and collected using local database registry of the unit in the duration between the year 2016 and 2020. Patients whose records had missing data were excluded from the study.

**Results:** A total of 274 MS patients' records were included. There was no significant correlation between the Expanded Disability Status Scale (EDSS) score and the number of relapses in the first 2 years of disease duration. Also the correlation between the EDSS score and the time from the first presenting symptom to the start of DMT treatment showed weak positive correlation. There was a significant difference when comparing the EDSS across the different first presenting symptoms. The mean EDSS with sensory symptoms was lower than the mean EDSS with motor symptoms.

**Conclusion:** The results of this study revealed that there is no relation between early relapse rate and later EDSS. Other clinical characteristics as time to start treatment and first presenting symptom showed significant relation to the current disability score.

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**Keywords:** Multiple sclerosis; expanded disability status scale, MS progression, disease modifying therapies, drug switching.

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### INTRODUCTION

MS is a progressive neurodegenerative disease that is considered the leading cause of non-traumatic disability among young and middle-aged people in many countries [1].

Early and appropriate treatment can markedly reduce disease activity and accumulation of disability to avoid many of the long-term economic and personal expenses that result from unnecessary irreversible disability [2]. The most common reason for drug switching is a poor response to DMT, and the clinical response that is

measured by disease activity in the form of relapses and disability progression [3, 4].

Baseline disease features related to disability progression need to be addressed to achieve early accurate prognosis. Considering that EDSS is the gold standard to measure disability and worsening as it is widespread used and accepted by both clinicians and regulators [5]. The purpose of our study is to investigate the clinical features related to the EDSS in a group of MS patients underwent

treatment failure and switched between two or more DMTs.

## SUBJECTS AND METHODS

### Study design and setting

This is a cross-sectional study based on records of MS patients who had been actively receiving available DMTs at the MS unit of Nasser Institute Hospital for Research and Treatment. The data were reviewed and collected using local database registry of the unit in the duration between 2016 and 2020. Patients whose records had missing data were excluded from the study.

The requirements of Nasser Institute Hospital Ethics Committee were fulfilled. In this study, a total of 274 patients' records fulfilled the inclusion criteria of the study and switched from one DMT to another DMT or more and were included in the study.

### The inclusion criteria are as follows:

1. MS patients diagnosed according to the McDonald criteria <sup>[6, 7]</sup>,
2. Patients who had been actively receiving DMTs and underwent switching between more than one drug.
3. Both sexes and all age groups.

### The exclusion criteria are as follows:

1. Primary progressive MS patients.
  2. Patients whose records were inactive for more than six continuous months, and
  3. Patients whose records had missing data related to the study.
- The baseline demographics of the patients were collected. Clinical history was collected including initial presenting symptom, and the time between the first presenting symptom and the start of the treatment (grouped into 4 categories).
  - Number of relapses in the first two years of disease duration due to its prognostic value.
  - Worsening of disability was assessed using the current examinations of patients' stable EDSS score <sup>[9]</sup>, performed through an evaluation far at least 30 days from any clinical relapse <sup>[5]</sup>.
  - The first presenting symptoms of the disease were categorized into six types according to the function affected; motor, sensory, visual, cerebellar, diplopia and other less commonly presented symptoms as fatigue and sphincteric (urinary and faecal) symptoms.

### Statistical analysis

Descriptive statistics were done in terms of frequencies and relative frequencies for the categorical variables. Numeric variables were presented in the form of mean and standard deviation. One way ANOVA to compare the EDSS score across the five most common presenting

symptoms. Correlation between the EDSS score and time from the first symptom to the start of treatment and correlation between EDSS and the number of relapses in first 2 years of disease duration were studied using Spearman's correlation. IBM SPSS statistics software, version 26, was used for the analysis and p-value <0.05 was considered statistically significant.

## RESULTS

The study included 274 MS patients' records receiving treatment and underwent switching between two or more DMTs. As shown in table (1), 208 (75.9%) were females and 66 (24.1%) were males. The time from the first symptom to the start of treatment were grouped into five categories, the major proportion of the patients (118 (43.1%)) were from 1 to 5 years, then 74 patients less than 1 year, 54 patients from 6 to 10 years and 28 patients more than 10 years to start MS specific therapy.

The most common first presenting symptoms of switching MS patients were the motor symptoms (97 (35.4%)), followed by visual impairment symptoms (22.6%), and sensory (21.5%), then cerebellar (12.4%), diplopia (6.6%) symptoms and other least reported symptoms (1.4%).

The number of relapses in the first 2 years from disease duration ranged from 1 to 5 relapses, (42.7%) of the patients reported 2 relapses in the first two years, followed by one relapse in (30.7%) of patients, then three relapses in (16.8%), four relapses in (8%) and five relapses in only 5 patients.

The most common discontinued drug was INF beta 1A sc with 143 (52.2%) of patients, followed by INF beta 1B sc (33.2%), and the least discontinued drugs were Glatiramer acetate, Dimethylfumarate and Rituximab. The most common drug to be switched to is Fingolimod (60.9%), followed by INFs beta 1A sc and im, and the least common one is Natalizumab (0.8%).

In table (2), the mean age was (35.4±8.2) and the mean disease duration (8.1±5.2). The mean EDSS among the sample was (3.6 ±1.1). The mean time to switch between the DMTs across the sample was (1.9±1.5) year.

Table (3) shows no significant correlation between the EDSS score and the number of relapses in first 2 years of disease duration.

The correlation between the EDSS score and the time from first symptom to the start of DMT (groups) showed weak positive correlation between them ( $\rho=0.26$ ) as shown in figure (1). Also there were significant difference when comparing the EDSS across the different first presenting symptoms types as shown in table (4) and figure (2). The results showed that the EDSS score for patients with sensory first presenting symptoms (3.4±1.0) was lower than the EDSS score for patients presenting with motor symptoms (4.08±0.96).

**Table (1): Clinical characteristics of the patients**

Parameter		No. (%)
<b>Gender</b>	Male	66 (24.1)
	Female	208 (75.9)
<b>Time from first symptom to the start of treatment</b>	Less than 1 year	74 (27)
	From 1 to 5 years	118 (43.1)
	From 6 to 10 years	54 (19.7)
	More than 10 years	28 (10.2)
<b>First presenting symptom of the disease</b>	Motor	97 (35.4)
	Sensory	59 (21.5)
	Visual	62 (22.6)
	Cerebellar	34 (12.4)
	Diplopia	18 (6.6)
	Others***	4 (1.4)
<b>Number of relapses in first 2 years of disease duration</b>	1	84 (30.7)
	2	117 (42.7)
	3	46 (16.8)
	4	22 (8)
	5	5 (1.8)
<b>Previous DMT**</b>	INF* 1A IM	33 (12.0)
	INF 1B SC	91 (33.2)
	INF 1A SC	143 (52.2)
	Dimethyl fumarate	1 (0.4)
	Fingolimod	4 (1.5)
	Rituximab	1 (0.4)
	Glatiramer acetate	1 (0.4)
<b>New DMT</b>	INF 1A IM	26 (9.5)
	INF 1B SC	13 (4.7)
	INF 1A SC	26 (9.5)
	Teriflunomide	4 (1.5)
	Dimethyl fumarate	7 (2.6)
	Fingolimod	167 (60.9)
	Rituximab	25 (9.1)
	Ocrelizumab	4 (1.5)
	Natalizumab	2 (0.8)

\* Interferon, \*\* Disease modifying therapy, \*\*\*4 cases has diverse symptoms were grouped in others.

**Table (2): Clinical characteristics of the patients**

Parameter	Mean ± SD
Age at the time of enrollment to the study	35.4 ± 8.2
Disease duration in years	8.1 ± 5.2
EDSS* score	3.6 ± 1.1
Time to switch from previous drug to the new one in years	1.9 ± 1.5

\*Expanded Disability Status Scale

**Table( 3): Correlations of EDSS and other main clinical parameters**

Correlation with EDSS	r	P-value
Number of relapses in first 2 years from disease onset	0.023	0.705
Time from first symptom to the start of treatment	0.259	0.001*

\* Spearman’s correlation was used

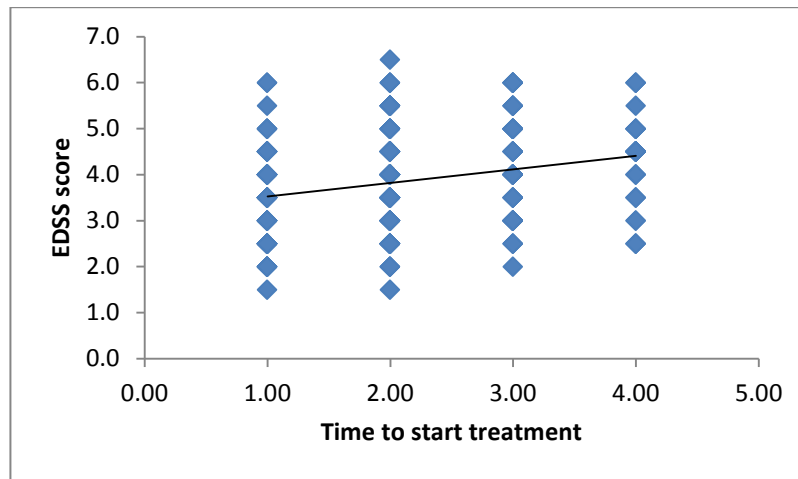


Figure (1): Scatter plot for the EDSS and the time to start treatment

Table (4): Comparison of the EDSS score between the common first presenting symptoms

Symptom	N**	Mean ± SD	P-value
Motor	97	4.08 ± 0.96	0.002*
Sensory	59	3.41 ± 1.00	
Visual	62	3.73 ± 1.02	
Cerebellar	34	4.00 ± 1.13	
Diplopia	18	3.97 ± 1.06	

\* One way ANOVA was used, \*\*The 4 cases that has diverse symptoms were excluded in this table

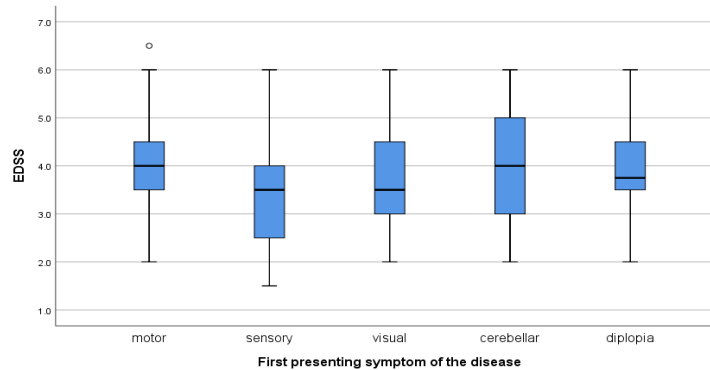


Figure 2. Boxplot for the EDSS across the different presenting symptoms

**DISCUSSION**

This study investigated primarily three baseline clinical features that can be related to disability status (measured by the EDSS) in MS patients who underwent switching between DMTs.

In the current study, no significant correlation was found between the EDSS and the number of early relapses in the first two years of disease duration. In other studies, the significance of relapses as prognostic factor for disability progression has been debated. Some studies demonstrated that higher relapse rate in the first two years of disease duration was strongly correlated with disability accumulation and used as a predictor of rapid progression [10-12]. Some studies showed that frequent early relapses (during the first two and five years from onset) predict a more rapid disease evolution [13-16]. Also,

early attacks were shown to exert no significant effect on disease evolution [13, 16], and that different number of relapses after year 2 and of total relapses before progression had the same chance to attain high disability endpoints [16].

We found in this study that EDSS score is significantly correlated with the first presenting symptom. The score was lower for patients with sensory symptoms and higher with motor symptoms.

Our results agreed with that the first clinical presentation of MS affects the patient EDSS, patients with visual and sensory presentation had commonly lower EDSS, compared to patients with motor presentation had commonly higher EDSS [17]. Initial disease onset with motor, cerebellar or brainstem symptoms correlated with

a higher risk of rapid accumulation of moderate disability, but it didn't affect the late disease evolution<sup>[14, 15]</sup>. Also Malpas et al., reported presence of pyramidal signs in the first year of disease duration was predictive of EDSS progression  $\geq 6$  within 10 years<sup>[18]</sup>. On the other hand, there was an evidence of disagreed with that the first attack symptoms were predictive of increase in EDSS [19].

Moreover, this study showed a weak positive correlation between the EDSS score and time from the first symptom to the start of treatment.

This result was consistent with multiple studies confirmed that patients who started DMT later reached an EDSS score of 6 more quickly compared to patients who started early, and this delay was associated with clinical deterioration and showed a tendency to shorten time to death<sup>[20-22]</sup>.

## CONCLUSION

Results of this study revealed a weak positive significant correlation between the EDSS and the time to start treatment. These findings signify the value of initial baseline clinical features of the patients and the need for further research studies that could detect early fine changes and help to guide initial clinical decisions of MS patients' treatment.

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## REFERENCES

1. **Federation M S I.** Atlas of MS 2013: Mapping multiple sclerosis around the world. *Mult Scler Int Fed.*1-28, 2013.
2. **Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G et al.** Brain health: time matters in multiple sclerosis. *Multiple sclerosis and related disorders.* 9, S5-S48, 2016.
3. **Miller A E, Wolinsky J S, Kappos L, Comi G, Freedman M S, Olsson T P et al.** Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Neurology.* 13(10):977-986, 2014.
4. **Saccà F, Lanzillo R, Signori A, Maniscalco G T, Signoriello E, Lo Fermo S et al.** Determinants of therapy switch in multiple sclerosis treatment-naïve patients: a real-life study. *Multiple Sclerosis Journal.* 25(9):1263-1272, 2019.
5. **Inojosa H, Schriefer D, and Ziemssen T.** Clinical outcome measures in multiple sclerosis: a review. *Autoimmunity reviews.* 19(5): 102512, 2020.
6. **Polman C H, Reingold S C, and Banwell B.** Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann. Neurol.* 69 (2): 292-302, 2011.
7. **Thompson A J, Banwell B L, Barkhof F, Carroll W M, Coetzee T, Comi G et al.** Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 17:162–173, 2018.
8. **Kurtzke J.** Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 33(11):1444-1452, 1983.
9. **Weinshenker B G, Bass B, Rice G P A, Noseworthy J, Carriere W, Baskerville J et al.** The natural history of multiple sclerosis: a geographically based study: I. Clinical course and disability. *Brain.* 112(1):133-146, 1989.
10. **Weinshenker B G, Rice G P A, Noseworthy J H, Carriere W, Baskerville J, and Ebers G C.** The natural history of multiple sclerosis: a geographically based study: 3. Multivariate analysis of predictive factors and models of outcome. *Brain.* 114(2), 1045-1056, 1991.
11. **Confavreux C, Vukusic S, and Adeleine P.** Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain.* 126(4):770-782, 2003.
12. **O'Connor P W, Lublin F D, Wolinsky J S, Confavreux C, Comi G, Freedman M S et al.** Teriflunomide reduces relapse-related neurological sequelae, hospitalizations and steroid use. *Journal of neurology.* 260(10):2472-2480, 2013.
13. **Kalincik T, Buzzard K, Jokubaitis V, Trojano M, Duquette P, Izquierdo G et al.** Risk of relapse phenotype recurrence in multiple sclerosis. *Multiple Sclerosis Journal.* 20(11):1511-1522, 2014.
14. **Gettings E J, Hackett C T, Schramke C J, Scott T F.** Specific clinical phenotypes of relapsing multiple sclerosis based on disease activity. *Multiple Sclerosis Journal.* 20:233-233, 2014.
15. **Lublin F D, Cutter G, Giovannoni G, Pace A, Campbell N R, Belachew S.** Natalizumab reduces relapse clinical severity and improves relapse recovery in MS. *Multiple sclerosis and related disorders.* 3(6):705-711, 2014.
16. **Hussein H M, Aggag M F, Mohamed W O, Tharwat M E, and Mahmoud A M.** demographic, clinical and paraclinical characteristics of a sample of egyptian multiple sclerosis (ms) patients attending ms clinic in al-azhar university hospitals. *Al-Azhar Medical Journal.* 48(4):387-396, 2019.
17. **Malpas C B, Manouchehrinia A, and Sharmin S.** Early clinical markers of aggressive multiple sclerosis. *Brain J. Neurol.* 143 (5):1400–1413, 2020.
18. **Uludağ İ F, Kaya A, Demirtaş B S, Tiftikçioğlu B İ, and Zorlu Y.** Early Clinical Predictors of Disability in Multiple Sclerosis. *Journal of Neurology.* 21:22-6, 2015.
19. **Goodin D S, Traboulsee A, Knappertz V, Reder A T, Li D, Langdon D et al.** Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon  $\beta$ -1b trial in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry.* 83(3):282-287, 2012.
20. **Chalmer T A, Bagesen L M, Nørgaard M,**

- Koch-Henriksen N, Magyari M, and Sorensen P S.** Early versus later treatment start in multiple sclerosis: a register-based cohort study. *Eur J Neurol.* 25: 1262-e110, 2018.
21. **Harding K, Williams O, Willis M, Hrastelj J, Rimmer A, Joseph F et al.** Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. *JAMA neurology.* 76(5):536-541, 2019.
22. **He A, Merkel B, Brown J W L, Ryerson L Z, Kister I, Malpas, C. B et al.** Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *The Lancet Neurology.* 19(4):307-316, 2020.

## الملخص العربي

حالة الإعاقة بين مرضى التصلب المتعدد و علاقتها بالسمات السريرية والأدوية المتبدلة  
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### ملخص البحث

**الخلفية:** التصلب المتعدد هو مرض عصبي تدريجي يسبب إعاقة ثابتة. و السبب الرئيسي للتبدل بين العلاجات المعدلة للمرض بالنسبة للتصلب المتعدد هو الاستجابة دون المستوى الأمثل في شكل هجمات أو تطور الإعاقة كنتائج سريرية رئيسية.

**الهدف:** تهدف هذه الدراسة إلى تحديد السمات الإكلينيكية الأساسية المرتبطة بحالة الإعاقة في صفوف مرضى التصلب المتعدد الذين تعرضوا للتبدل بين اثنين أو أكثر من العلاجات المعدلة للمرض.

**الطرق:** هذه الدراسة عبارة عن دراسة مقطعية تستند إلى سجلات مرضى التصلب المتعدد ممن تلقوا العلاجات المعدلة للمرض المتاحة في وحدة التصلب المتعدد الخاصة بمستشفى معهد ناصر للبحوث والعلاج. تمت مراجعة و جمع البيانات باستخدام سجل قاعدة البيانات المحلية للوحدة في المدة بين عام 2016 و 2020. تم استبعاد سجلات المرضى التي تفتقر إلى البيانات اللازمة للدراسة.

**النتائج:** شملت الدراسة ما مجموعه 274 من سجلات مرضى التصلب المتعدد. وتبين أنه لم يكن هناك ارتباط بين درجة وعدد الانتكاسات في أول سنتين من مدة المرض. كما أظهرت الدراسة ارتباطاً إيجابياً ضعيفاً بين درجة مقياس اتساع مدى الإعاقة والوقت من ظهور العرض الأول حتى بدء العلاج. علاوة على ذلك، كان هناك فرق كبير عند مقارنة مقياس اتساع مدى الإعاقة عبر مختلف الأعراض الأولية للمرض حيث كان متوسط مقياس اتساع مدى الإعاقة مع الأعراض الحسية أقل من متوسط المقياس مع الأعراض الحركية.

**الاستنتاجات:** كشفت نتائج هذه الدراسة أنه لا توجد علاقة بين معدل الانتكاس المبكر للمرض و مقياس اتساع مدى الإعاقة مؤخراً في المرض. أظهرت الخصائص السريرية الأخرى مثل وقت بدء العلاج و الأعراض الأولية ارتباطاً بدرجات الإعاقة الحالية.

**الكلمات المفتاحية:** التصلب المتعدد، مقياس اتساع مدى الإعاقة، تطور التصلب المتعدد، العلاجات المعدلة للمرض، تبديل الأدوية.

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