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Research Article

Association of Correlating Factors in the Progression of Irreversible Disability in Multiple Sclerosis

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ABSTRACT

Objective: Multiple Sclerosis (MS) is the leading cause of acquired motor disability in young adults. The increase in disability follows the progression of the disease and imposes impact on the affected person, thereby causing a permanent multidimensional handicap. The identification of the factors associated with the evolution towards an irreversible handicap is important for an adequate therapeutic management. This study explored to identify non-modifiable factors associated with progression to irreversible disability in patients with MS.

Material and methods: This is a prospective collection study that was carried out in the physical medicine and rehabilitation departments of the University Hospital of Oran and the Regional Military University Hospital of Oran (HMRUO), between January 2017 and December 2019. For the main analysis, we retained an Expanded Disability Status Scale (EDSS) score, if the patient had same functional status during the last six months.

Results and discussion: This study included 103 MS cases, including 72 women and 31 men, with a mean age at onset of symptoms of 31.83 years and a mean EDSS of 5.12 ± 1.97.

The progression of the disability assessed by the EDSS scale is related to baseline characteristics such as gender, age at advanced onset and progressive form of MS. We did not find a correlation between the severity of the handicap and the place of birth and/or residence.

Our results are unanimous in the literature for certain parameters, and the same is not true for others.

Conclusion: Non-modifiable factors in MS, such as age, gender, place of birth and/or residence are important predictors of disability and should alert the clinician to appropriate and specific management even at an early stage of the disease.

Keywords: Multiple sclerosis, disability, assessment, EDSS

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INTRODUCTION

Multiple Sclerosis (MS) is a chronic incurable disease of the central nervous system, combining an autoimmune inflammatory component and a neurodegenerative component. The respective proportions of these two components account for the particularities of the disease's evolution, with a variable combination of more or less resolving relapses and progressive worsening of disability. MS affects over 2.8 million people worldwide. Its epidemiology is dominated by a north-south gradient in the northern hemisphere, and a south-north gradient in the southern hemisphere (Pauline MA, 2013; Martin JE, *et al.*, 2016). On average, the onset of the disease occurs at the age of 30, at a crucial time in a person's personal, professional and social life. It is the leading cause of non-traumatic disability among young people in many developed countries. Despite undeniable therapeutic advances, nothing can yet prevent the progression of the disease towards progressive and inexorable disability. Identifying the factors associated with progression to irreversible disability is an important step towards appropriate management.

MATERIALS AND METHODS

General information

This is a descriptive, prospective, bicentric study of MS patients, which was carried out in the Physical Medicine and Rehabilitation Departments Of The University Hospital Centre Of Oran (CHUO) and Regional Military University Hospital of Oran (HMRUO) and the study population included all the MS patients referred to our level for rehabilitative care. This study was conducted for 2 years and 6 months (from January 2017 to June 2019).

Inclusion criteria

Patients with definite MS; patients who were diagnosed according to the Mac Donald 2005/2010 criteria and patients of age 18 or older were included in the study.

Exclusion criteria

Similarly, patients who were diagnosed with the disease within the last 6 months; patients having mental and cognitive disability/ with low comprehensibility; patients with the presence of severe psychiatric pathology, inflammatory, infectious or cardiac disease that has not been stabilized or treated and patients who have undergone surgery in the past (less than six months) were excluded from the study.

Method

For the main analysis of MS progression, Expanded Disability Status Scale (EDSS) residual disability levels at the last consultation were grouped into 4 categories-

- EDSS<4 was denoted as minimal disability or the patient retains autonomous walking despite some impairments.
- EDSS score between 4-6 depicted moderate disability which corresponds to a progressive limitation of walking perimeter, but without assistance or rest for distances of less than 500 meters.
- EDSS score between 6-7 corresponds to severe disability which means the ability to walk with unilateral or bilateral support for no more than 100 m.
- EDSS ≥ 7 denoted severe disability where the patient walks in a wheelchair with progressive loss of the ability to manipulate it.

We withheld the EDSS score from the patient if he had the same functional status for the last six months (notion of irreversible disability).

Base-line characters

Age: The mean age of patients in our study was 41.57 ± 11.22 years, with a minimum age of 19 years and a maximum age of 69 years. 56.3% of patients were over 40 years of age (*Figure 1*). While the mean age of patients in our series at diagnosis was 35.23 ± 11.41 years, with a minimum age of 10 years (1 patient) and a maximum age of 69 years (1 patient), and the mean age of onset was, 31.83 ± 11.52 years and ranged from (10-65) years (*Table 1*). Statistical analysis showed a significant relationship between age and severity of disability (p=0.015). We found that 17 (89.4%) of the 19 patients with severe disability were over 40 years of age, and 13 (81.25%) of the 16 patients under 30 years of age had minimal to moderate disability (EDSS<6) (*Table 2*). A highly significant relationship was found between duration of progression and age of onset according to the log rank method (p<0.001). The duration of disease progression was very short in patients who had their onset symptoms at an advanced age (*Table 3*).

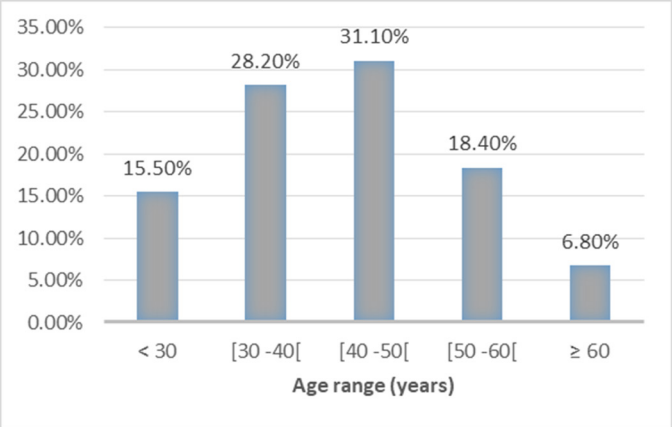

Figure 1: Distribution according to current age

Table 1: Severity of disability by current age

Age (y)	Minimal disability	Moderate disability	Important disability	Severe disability	Total
<30	6	7	2	1	16
(30-40)	8	6	14	1	29
(40-50)	7	3	12	10	32
(50-60)	7	3	5	4	19
≥ 60	0	2	2	3	7
Total	28	21	35	19	103

Table 2: Distribution according to severity of disability at the EDSS

Severity of disability and EDSS	Effective	Percentage (%)
Minimal disability (EDSS<4)	28	27.2
Moderate disability (EDSS=4-6)	21	20.4
Important disability (EDSS=6-7)	35	34.0
Severe disability (EDSS ≥ 7)	19	18.4
Total	103	100.0

Table 3: Estimated duration of evolution by age of onset

Onset of age (y)	Evolution time (Age)	
	Average (y)	Median (y)
<18	23.467	26.000
18-29	16.920	17.000
30-39	11.110	11.000
40-49	10.943	12.000
≥ 50	4.771	4.000
Global	14.698	14.000

Gender: Analysis of the results shows a predominance of females. Of the 103 patients, 71 were women (68.9%), while men accounted for 31.1% (32 patients). The female/male gender parity ratio was 2.21. Disability appears to be more severe in men. We found that the mean EDSS for men was 5.48 ± 1.81, while for women it was 4.95 ± 2.027, and that the F/H gender ratio for the minimal disability class was 3.67, while for the severe disability class the gender ratio was 1.69 (*Table 4*).

Table 4: Distribution of disability severity by gender

Disability level	Female (F)	Male (M)	Total	F/M gender parity ratio
Minimal disability	22	6	28	3.67
Moderate disability	14	7	21	2
Important disability	22	13	35	1.69
Severe disability	13	6	19	2.16
Total	71	32	103	2.21

It was also noted that 59.3% of men had a significant to severe disability. The median time to reach EDSS=6 (significant disability) for our patients, calculated by the Kaplan and Meier method, was 23 years, whereas it was 25 years for women and 17 years for men, meaning that disability progression is faster in men with MS (*Figure 2*).

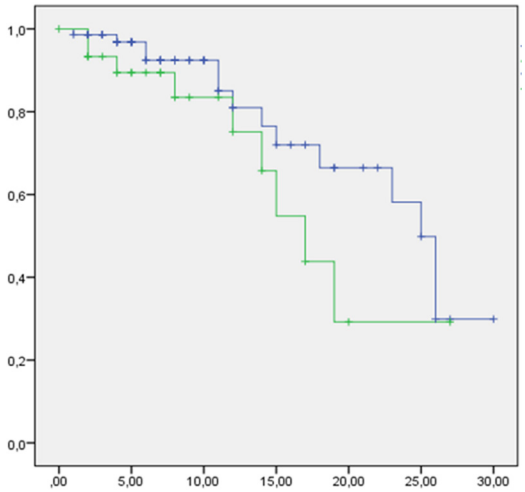

Figure 2: Estimated duration of progression to severe disability by gender
Note: (—): Female and (—): Male

Place of birth and residence: We had 70 patients (68%) from Wilayas in the North of the country (the coast), 31 patients (30.1%) from the high plateau and only 2 patients from the Sahara. However, most patients (80%) in our series lived on the coast (*Figure 3*). Overall, the statistical analysis did not find a correlation between severity of disability and place of birth and/or residence, but it should be noted that over 57% of patients who had lived in the littoral region had a significant to severe disability, compared with 37.5% for patients living in the highlands and only 20% for patients living in the South (*Table 5*).

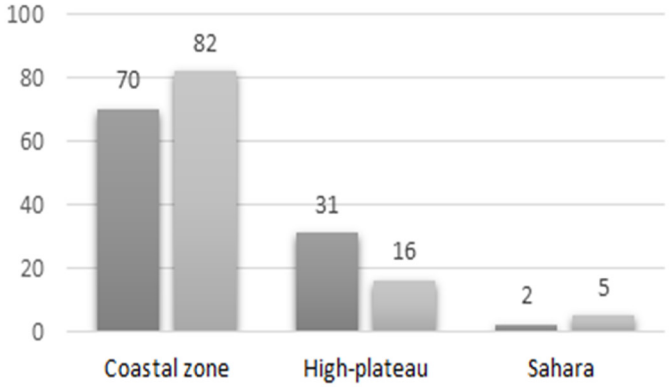

Figure 3: Distribution of MS patients by place of birth and residence
Note: (▪): Place of birth and (▪): Place of residence

Table 5: Severity of disability by place of birth and residence

Wilaya situation	Severity of disability (EDSS)				Total
	Minimal disability	Moderate disability	Important disability	Severe disability	
The coast (B-R)	17-20	13 -15	27-30	13-17	70-82
Highland (B-R)	11-6	45.389	8-5	5-1	31-16
Sahara (B-R)	0-2	45.323	0-0	1-1	2-5
Total	28	21	35	19	103

Note: B: Birth and R: Residence

Clinical form

In our study, the clinical form was remittent in 52.4% of patients. Over half the women (57.7%) had a relapsing-remitting form, while over half the men (59.3%) had a progressive form (*Table 6*). The female/male gender ratio in relapsing-remitting MS was 3.15, while in Secondarily Progressive (SP) form was 1.58 and for Progressive Primary (PP) form=1.42. According to EDSS, the mean EDSS scale in our series was 5.12 ± 1.97, with a minimum of 1 and a maximum of 9.

Table 6: Distribution of MS clinical forms by gender

Clinical form	Women	Men	Total (%)
RR	41 (75.9%)	13 (24.1%)	54 (52.4)
SP	19 (61.3%)	12 (38.7%)	31 (30.1)
PP	10 (58.8%)	7 (41.2%)	17 (16.5)
Benign form	1 (100%)	0 (0.0%)	1 (1.0)
Total	71 (68.9%)	32 (31.1%)	103 (100)

Note: RR: Relapsing Remitting; SP: Secondarily Progressive and PP: Progressive Primary

Progression of clinical form

Statistical analysis revealed a highly significant correlation between worsening disability on the EDSS scale and the progressive form of MS ($p<0.001$). The mean EDSS in MS patients with RR form was lower than in patients with progressive forms (PP and SP) (*Table 7*).

Table 7: Average EDSS by MS form

Sclerosis types	n	EDSS average	Deviation	Minimum	Maximum	F	p
RR	54	4.04	1.91	1.00	7.50	18.551	0
SP	31	6.32	1.03	4.00	9.00		
PP	17	6.47	1.29	4.00	8.50		
Total	102	5.12	1.97	1.00	9.00		

Note: RR: Relapsing Remitting; SP: Secondarily Progressive and PP: Progressive Primary

A significant relationship was also found between duration of evolution and the progressive form of MS according to the log rank method ($p=0.006$).The relapsing-remitting MS form (blue) evolves more slowly towards significant disability (EDSS ≥ 6) than the SPMS (green) and PPMS (brown) forms (*Figure 4*).

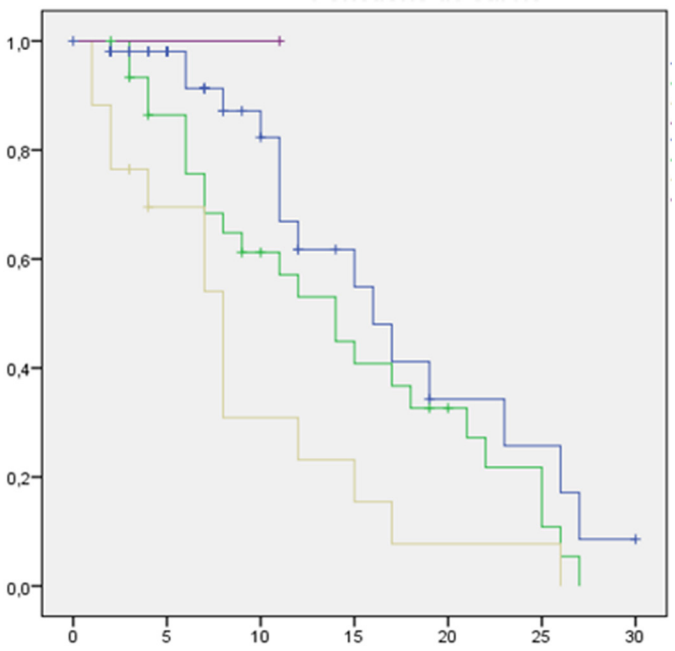

Figure 4: Duration of evolution according to the clinical form of MS
Note: (—): RR; (—): SP; (—): PP and (—): Benign

Statistical analysis

Uni- and multivariate-analysis was performed using Statistical Package for Social Sciences (SPSS) 20 software. However, the Cox model retained age of onset as a prognostic factor for median EDSS disability delay ≥ 6 (*Table 8*).

Table 8: Multivariate analysis by Cox model

Multivariate analysis	B	Standard Error (SE)	Wald	Dof	Significance	Exp (B)
Onset of age	0.058	0.016	13.398	1	0	1.059

Note: B: Equation coefficient ; Dof: Degree of freedom and Exp (B): Odds ratio

RESULTS AND DISCUSSION

Age of onset is one of the clinical factors most strongly associated with disease progression. Thus, it is commonly accepted that an earlier age of onset is associated with a slower progression of disability and therefore a better prognosis (Renoux C, *et al.*, 2007; Confavreux C, *et al.*, 2003). We did not find a correlation between age of onset and severity of EDSS score, but we did find a highly significant relationship between age of onset and mean time to major to severe disability (EDSS ≥ 6) according to the Kaplan Meier-Log Rank survival curve ($p<0.001$).

Our results are in line with the literature, with studies by Renoux C, *et al.*, 2007 and Confavreux C, *et al.*, 2003 reporting that patients with an initial symptomatology at an advanced age had a short duration of evolution with a more rapid progression of disability (Tremlett H, *et al.*, 2008; Myhr KM, *et al.*, 2001).

The gender distribution of our patients shows a clear female predominance, with 68.9% women vs. 31.1% men, corresponding to an F/M gender ratio of 2.23 (*Table 3*). This female predominance is similar to that found in the literature (Drai R, 2018; Scalfari A, *et al.*, 2010, Zakaria M, *et al.*, 2016; Tremlett H, *et al.*, 2008; Myhr KM, *et al.*, 2001; Araqi-Houssaini A, *et al.*, 2014; Sidhom Y, *et al.*, 2015). In our study, we found that disability appears more severe in men, with a shorter duration of progression to significant disability. The mean EDSS for men was 5.48 ± 1.81, while for women it was 4.95 ± 2.027, and the F/M sex ratio for the minimal disability class was 3.67, while it was 1.69 for the major disability class. More than half the women (57.7%) had a remittent form, while more than half the men (59.4%) had a progressive form. It was also noted that 59.3% of men had significant to severe disability. Our results concur with those of most studies assessing prognosis, such as Briggs FB, *et al.*, 2019 who reported that EDSS score progression was greater for men when all stages of the disease were included (Myhr KM, *et al.*, 2001; Bergamaschi R, 2007; Schwendimann RN and Alekseeva N, 2007).

We found no statistically significant correlation between severity of disability and place of birth or residence, although we did note that over 57% of patients born and/or living in the coastal region had a significant to severe disability, compared with 37.5% for patients living in the highlands and only 20% for patients living in the Sahara. This result is in line with references (Lucas RM, *et al.*, 2015; Correale J and Farez MF, 2013) showing the protective effect of latitude, ultraviolet radiation and vitamin D (Climate for traveling) (www.climatsetvoyages.com). We also noted that the patients (1 male and 1 female) in our study who were born in the South and lived there presented their first symptoms at a very advanced age (>60 years), while the three patients who were born in the north and moved to the South as adults had minimal to moderate disability. This insufficient number does not allow us to conclude on the positive (protective) role of a stay in the Sahara, particularly on the evolution of disability and MS in general. We have not found any specific study of MS in the Algerian Sahara, and studies in this area would be necessary.

In our study, the dominant clinical form was RR remitting in 52.4% of cases, followed by SP in 30.1% and PP in 16.5%. Statistical analysis showed a highly significant correlation between worsening disability on the EDSS scale and the progressive form of MS. Indeed, the mean EDSS in patients with Relapsing-Remitting (RR) MS was lower than for other progressive forms (PP and SP). Our results concur with the studies of Drai R, 2018; Confavreux C and Vukusic S, 2006; Roxburgh RH, *et al.*, 2005, implying that relapsing-remitting MS forms have a better prognosis.

Over the last ten years, several teams have questioned the relationship between relapses and the accumulation of disability. Studies have shown that, once disability has set in and progression is underway, previous relapses and those superimposed on progression have little or no influence on the subsequent evolution of disability (Confavreux C, *et al.*, 1980). Thus, on average, forms with remittent onset progress more slowly towards different levels of disability than those with progressive onset.

In our study, the average time between disease onset and EDSS scores 3, 4 and 6 scores at the last visit was 5.83/6/12.65 years respectively. Compared with the literature, these times are similar to those found by Drai R, 2018 for EDSS 3 and 4, but longer for EDSS 6. However, the delays remain relatively short compared with other international studies, possibly reflecting the severity of MS in a large number of our patients. And this is in line with the results reported in studies of patients of North African ethnic origin living in France, who had a more severe disease phenotype than those of French origin, so the influence of preclinical geographical area is a new prognostic factor (Jeannin S, *et al.*, 2007; Lebrun C, *et al.*, 2008; Sidhom Y, *et al.*, 2017).

The median survival time from the onset of MS to the EDSS 6 score was estimated at 17 years in our series by the Kaplan-Meier technique, which is considered close to that found in the literature (Scalfari A, *et al.*, 2010; Sidhom Y, *et al.*, 2014; Araqi-Houssaini A, *et al.*, 2014; Leray E, *et al.*, 2010) (*Table 9*). On the other hand, it is longer in the work of the Blida team (Drai R, 2018). This difference in results can be explained by our smaller sample size, and by our lack of knowledge of the exact date of transition to this stage of disability (EDSS=6), since this is a cross-sectional study, in addition to the difference in statistical methods and software used for data analysis.

Table 9: Average time to reach EDSS 6 compared with other studies in the literature

Study of EDSS 6 delay	References
18	n=806 (Scalfari A, et al., 2010)
18	n=2054 (Leray E, et al., 2010)
15	n=437 (Sidhom Y, et al., 2014)
7	n=741 (Drai R, et al., 2018)
17	n=103 (Present study)

CONCLUSION

MS is a heterogeneous disease, with unpredictable symptoms, general course and functional prognosis. It is the leading cause of acquired motor disability in young adults.

The prevalence of this disease is clearly increasing in our country. And its

evolutionary profile appears to be more severe. The consequences of the disease in terms of disability, handicap and impact on daily life are considerable.

Assessment of functional disorders and disability secondary to MS is the key to appropriate rehabilitation management.

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