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Non-Modifiable Factors Associated with Progression to Irreversible Disability in Multiple Sclerosis Patients

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ABSTRACT

Introduction: 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 on those affected a permanent multidimensional handicap. The identification of the factors associated with the evolution towards an irreversible handicap is important for an adequate therapeutic management.

Objective: Identify the 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 HMRU of Oran, between January 2017 and December 2019. For the main analysis, we retained an EDSS score (Expanded Disability Status Scale) for the patient if he had the same functional status during the last six months.

Results/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: male 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 and 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.

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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 [1, 2].

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.

Objective

To identify non-modifiable factors associated with progression to irreversible disability in MS patients.

Materials and Methods

Type of Study

This is a descriptive, prospective, bicentric study of MS patients, carried out in the Physical Medicine and Rehabilitation departments of the university hospital center of Oran (CHUO) and the Regional Military University Hospital of Oran (HMRUO).

Study Population

All MS patients referred to our level for rehabilitative care.

Inclusion Criteria for this Study

- Patients with definite MS, diagnosed according to the Mac Donald 2005 /2010 criteria.
- 18 years of age or older.
- Whatever the form, whatever the stage of the disease.

Non-Inclusion Criteria
- A relapse of the disease within the last 6 months.
- Cognitive state incompatible with understanding instructions.
- Presence of severe psychiatric pathology, inflammatory, infectious or cardiac disease that has not been stabilized or treated.
- Recent surgical history (less than six months).

Study Duration
Two (02) years and 06 months, from January 2017 to June 2019.

Uni- and multivariate analysis was performed using SPSS 20 software. For the main analysis of MS progression, Expanded Disability Status Scale (EDSS) residual disability levels at the last consultation were grouped into 4 categories:
- Minimal Disability EDSS < 4; or the patient retains autonomous walking despite some impairments.
- Moderate Disability EDSS = [4-6[; which corresponds to a progressive limitation of walking perimeter, but without assistance or rest for distances of less than 500 meters.
- Severe Disability EDSS= [6-7[, corresponding to the ability to walk with unilateral or bilateral support for no more than 100 m.
- Severe Disability EDSS ≥7, the patient walks in a wheelchair with progressive loss of the ability to manipulate it.

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

Results
Age
The mean age of patients in our series 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).

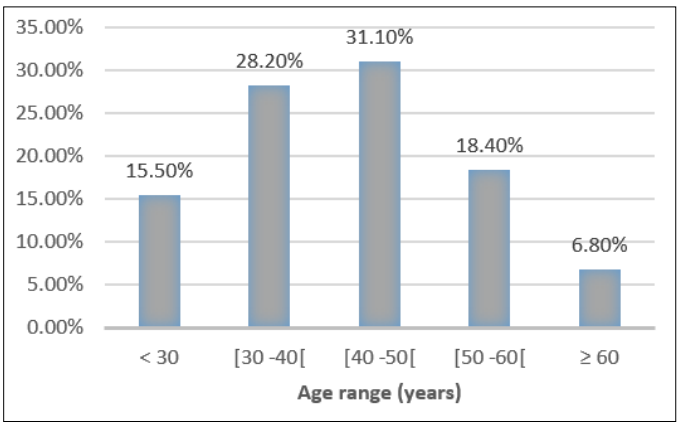

Figure 1: Distribution According to Current Age

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 case) and a maximum age of 69 years (1 case), and the mean age of onset was: 31.83 ± 11.52 years and ranged from 10 to 65 years.

Sex
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 sex ratio was 2.21.

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 2).

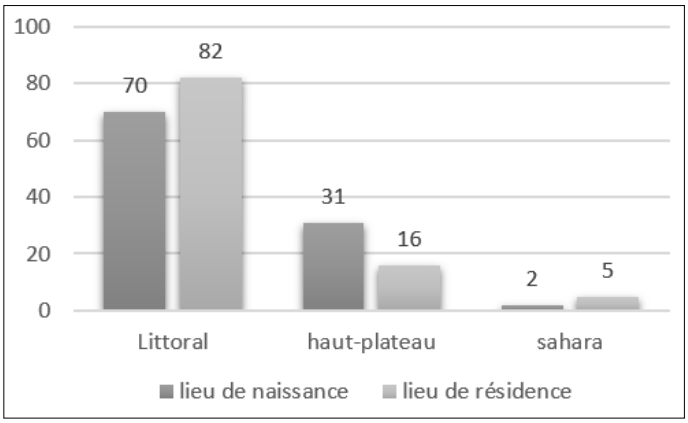

Figure 2: Distribution of MS Patients by Place of Birth and Residence

Clinical Form
In our study, the clinical form was remittent in 52.4% of cases. Over half the women (57.7%) had a relapsing-remitting form, while over half the men (59.3%) had a progressive form (Table 1). The sex ratio: female/male ratio in RRMS was 3.15, while in secondarily progressive form (SP) was 1.58 and for progressive primary form (PP) = 1.42.

Table 1: 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 (0,0%)	1 (1,0)
Total	71(68,9%)	32(31,1%)	103(100)

RR: Relapsing-Remitting, **SP:** Secondarily Progressive, **PP:** Progressive Primary

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.

We classified our patients according to disability status into four levels (Table 2)

Table 2: Distribution According to Severity of Disability at the EDSS

Severity of Disability	Effective	%
Minimal Disability EDSS < 4	28	27,2
Moderate Disability EDSS = [4-6[,	21	20,4
Importante Disability EDSS= [6-7[	35	34,0
Severs Disability EDSS ≥7	19	18,4
Total	103	100,0

Non-Modifiable Factors and Disability

Gender

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 sex ratio for the minimal disability class was 3.67, while for the severe disability class the sex ratio was 1.69 (Table 3).

It was also noted that 59.3% of men had a significant to severe disability.

Table 3: Distribution of Disability Severity by Gender

Severity of Disability	Women	Men	Total	F/H sex ratio
Minimal Disability	22	6	28	3,67
Moderate Disability	14	7	21	2
Importante Disability	22	13	35	1,69
Severs Disability	13	6	19	2,16
Total	71	32	103	2,21

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 3).

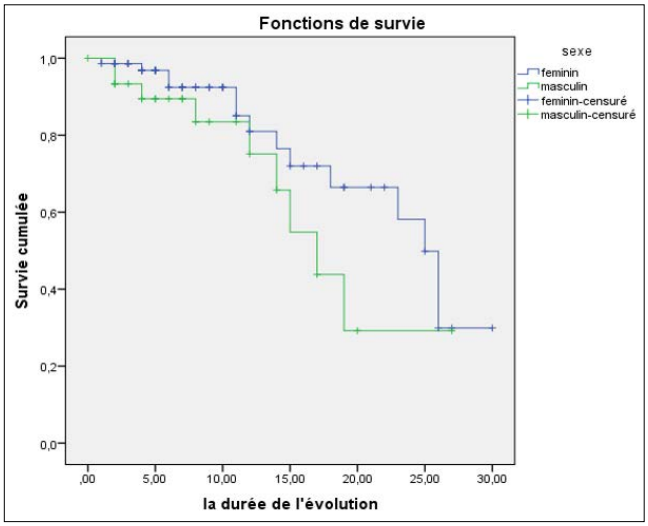

Figure 3: Estimated Duration of Progression to Severe Disability by Gender

Age

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 4: Severity of Disability by Current Age

Age	Minimal Disability	Moderate Disability	Importante 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

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 5).

Table 5: Estimated Duration of Evolution by Age of Onset

Age of Onset	Evolution Time	
	Average (years)	Median (years)
< 18 years	23,467	26,000
18 – 29 years	16,920	17,000
30 – 39 years	11,110	11,000
40 – 49 years	10,943	12,000
≥ 50 years	4,771	4,000
Global	14,698	14,000

Place of Birth and Residence

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 6: Severity of Disability by Place of Birth and Residence

Wilaya Situation	Severity of Disability (EDSS)				Total
	Minime Disability	Moderate Disability	Importante Disability	Severe Disability	
The Coast (B-R)	17 -20	13 -15	27 - 30	13 – 17	70 - 82
Highland (B -R)	11 – 6	7 - 4	8 - 5	5 - 1	31 – 16
Sahara (B -R)	0 – 2	1 - 2	0 - 0	1 - 1	2 – 5
Total	28	21	35	19	103

B: Birth. **R:** Residence.

Progressive 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, SP) (Table 7).

Table 7: Average EDSS by MS Form

	N	EDSS Average	Deviation	Min	Max	F	Sig. p
RR	54	4,04	1,91	1,00	7,50		
SP	31	6,32	1,03	4,00	9,00	18,551	,000
PP	17	6,47	1,29	4,00	8,50		
Total	102	5,12	1,97	1,00	9,00		

RR: Relapsing-Remitting, **SP:** Secondarily Progressive, **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 RRMS form (blue) evolves more slowly towards significant disability (EDSS≥6) than the SPMS (green) and PPMS (brown) forms (Figure 4).

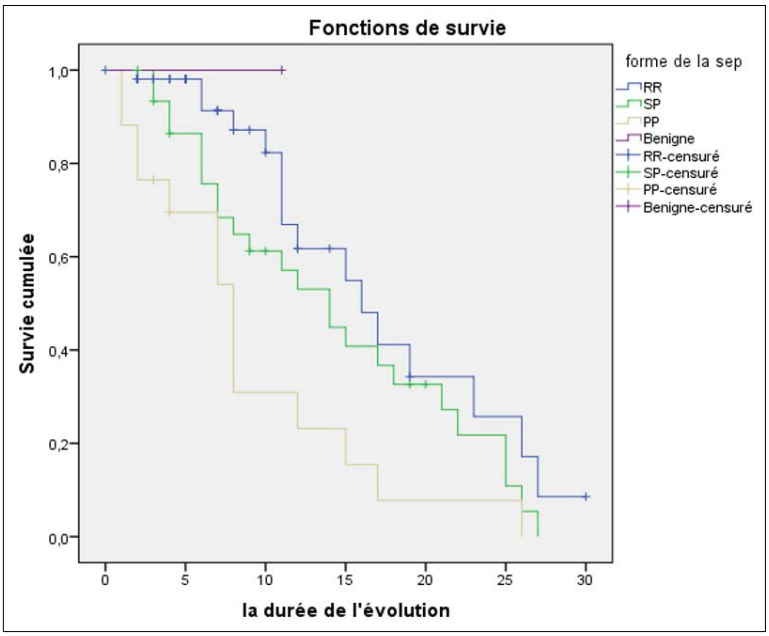

Figure 4: Duration of Evolution According to The Clinical form of MS

Multivariate Analysis

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

	B	S. E.	Wald	dol	Sig.	Exp(B)
Age of Onset	,058	,016	13,398	1	,000	1,059

B: Equation Coefficient. **S.E.:** Standard Error. **dof:** Degree of Freedom. **Exp (B):** Odds Ratio

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 [3].

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 and CONFARVEUX (4-7) reporting that patients with an initial symptomatology at an advanced age had a short duration of evolution with a more rapid progression of disability.

The gender distribution of our patients shows a clear female predominance, with 68.9% women versus 31.1% men, corresponding to an F/M sex ratio of 2.23. This female predominance is similar to that found in the literature [4-10].

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 et al. who reported that EDSS score progression was greater for men when all stages of the disease were included [5, 10, 11, 12].

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 showing the protective effect of latitude, ultraviolet radiation and vitamin D [13,14].

We also noted that the patients (01 male and 01 female) in our series 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 MS (RR) was lower than for other progressive forms (PP, SP). Our results concur with those of DRAI, CONFAVREUX, and SIDHOUM... who suggest that RRMS forms have a better prognosis [3, 15, 16].

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 [17]. 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 3, EDSS 4 and EDSS 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 in the DRAI study in Blida for EDSS 3 and 4, but longer for EDSS 6 (7 years for the DRAI series) [3].

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 [18-21].

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 (Table 9) [8, 22-25]. On the other hand, it is longer in the work of the Blida team [3].

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

Studies	Scalfari A et al. 2010 **N = 806**	Leray E et al. 2010 **N = 2054**	Sidhom Y.et al. 2014. **N = 437**	Drai R.et al 2018 **N=741**	Our Study 2020 **N =103**
EDSS 6 Delay	18	18	15	7	17

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.

Declaration of Interests

I declare that I have no conflicts of interest in relation to this article

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