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Impact of education and employment status on cognitive and physical disability in multiple sclerosis patients

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Abstract: Multiple sclerosis (MS) is the most common cause of non-traumatic disability in the young. Socioeconomic status – education and employment - are environmental factors that may influence MS genesis and disease course. We evaluate the impact of education and employment on cognitive and physical disability in a Romanian cohort of people with MS (pwMS). We analyzed data from 111 pwMS in our clinic. Isaacs set test (IST) and EDSS (Expanded Disability Status Scale) were used to evaluate cognition and physical function. Comparison of means and linear regression were used to characterize the relationship between education/employment and cognitive/physical evaluations. Individuals who fit in the 'high' education category had higher IST scores as compared to less educated subjects. Employed patients had significantly better IST scores. Linear regression showed that education can predict cognitive ($p<.05$, B=0.256, CI 0.042-0.469) and physical disability ($p<.001$, B= -0.43, 95% CI -0.607 to -0.264). EDSS scores were significantly lower in the 'high education' and employed groups. While the relationship between these factors is not yet fully comprehended, asking simple questions about one's socioeconomic status could represent useful tools in evaluating and managing pwMS.

Keywords: multiple sclerosis; cognition; Isaacs set test; disability; education; socioeconomic; employment.

1. Introduction

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system by mechanisms of inflammation, demyelination, and neurodegeneration that occur early in its course [1]. MS is usually symptomatic at a young age (20-40 years) and is the most common non-traumatic disability cause among young adults [1,2]. The classical clinical picture is characterized in most patients by relapses followed by remission periods (relapsing remitting MS - RRMS), a pattern that can last for years before being replaced by a progressive course (secondary progressive MS – SPMS) [2,3]. Cognitive decline is present from the early stages of MS and causes disability independently from somatic neurological status [4]. Information processing speed, attention, and memory are usually the most affected cognitive domains [5,6].

MS is a multifactorial disease: genetic and environmental agents are thought to interact in its genesis, vitamin D deficiency, smoking, obesity, and Epstein Barr Virus infection being well-studied factors that increase the risk of MS [1,3]. Recent studies consider socioeconomic status and level of education as possible predictors of developing MS. A case-control study from 2016 showed that completing more than 14 years of schooling is associated with a 41% lower risk of being diagnosed with MS [7]. The protective effect of education was not modified when data was adjusted for risk factors most commonly linked to MS [7].

Cognitive reserve in brain pathologies became a matter of interest in later years. Martins Da Silva et al. showed that educational status could be used as a determinant of cognitive reserve, as pwMS who reported higher levels of education performed better at cognitive evaluations [8]. This effect needs further research, since the representation of cognitive function in various studies is heterogeneous. Furthermore, only a few longitudinal studies explored this effect, with sometimes conflicting results. Conway et al. showed that pwMS holding a college or a graduate degree performed better than less educated subjects at baseline cognitive assessment [9]. In their study, graduate degree holders had lower odds of cognitive decline at 1- and 2-year follow-up, but the seemingly protective effect of education on cognitive performance was lost at 3-year follow-up, with no significant difference in the odds of worsening test results [9]. Their study also showed that employment status was positively influenced by education. Individuals holding either a college or a graduate degree kept higher odds of maintaining employment throughout the 3-year follow-up, regardless of their cognitive status (improved or worsened test results) [9]. In another study [10] lower education was associated with less chances of maintaining paid professional activity but not with the risk of disability pension or sickness absence within the specific professional categories (i.e., constructions or education), supporting a more complex relationship between the two.

Although cognition, fatigue, and quality of life are frequently “optional” or “second line” objectives of therapy, asking simple questions about one’s level of education and employment status could be an easily achievable approach to screen for risk of disability progression. We aim to assess the impact of these parameters on physical and cognitive disability and, therefore, their value as markers (or risk factors) to consider in the routine evaluation of MS patients.

2. Materials and Methods

2.1. Participants

The study was performed in the Clinical Rehabilitation Hospital in Iasi. We examined 172 patients over the age of 18, diagnosed with either clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS or primary progressive MS.

Sociodemographic data – age, sex, level of education, age of retirement (if applicable) – and test results for the Isaacs set test and the Expanded Disability Status Scale (EDSS) were extracted from medical records. We excluded patients diagnosed with other neurological or psychiatric comorbidities, students who have not yet completed high school, and stay-at-home persons who never worked.

2.2. Measures

The Isaacs Set Test (IST) is a semantic fluency test – it measures verbal abilities and executive function – as it engages one’s capacity to focus on a specific category and avoid repetition [11]. Semantic fluency relies mainly on temporal cortex networks [12]. IST is useful both in populations with severe cognitive decline and for persons that are highly functional mentally, as it can accurately predict dementia in elder populations [13] and it is sensitive to changes in the entire range of cognition [14].

IST is part of the brief battery of tests we use for the examination of cognitive functions of MS patients in our service. The test has a maximum of 40 points. The subject is successively given four categories for which he/she must enunciate ten elements (belonging to the given category) in a limited time interval (15 seconds). We chose to continue the test until due time regardless of the number of elements generated, assuming that producing more than the required number of elements might correlate with a better cognitive reserve.

2.3. Statistical analysis

Tests of normality were applied for each variable. We used log transformation for variables without a normal distribution.

We coded the employment status using two numeric variables: 0 for persons still working and 1 for those retired for medical reasons.

Education level was recorded in years of education. It was coded into three values, according to Romanian specifics in educational training , taking into account attendance and not graduation. Categories are: "low" - for the completion of up to 8 years of education, "standard" – for persons who attended high school or another equivalent form of education (9-12 years), and "high" for the continuation of one's studies, regardless of degree type or duration (≥13 years of education).

Comparison of means in the emergent groups was performed using nonparametric Mann-Whitney U and Kruskal-Wallis tests. We used linear regression to analyze the complex relationship between education, cognitive, and physical functions. We performed all statistical analysis with IBM's version 26 of the Statistical Product and Service Solutions (SPSS). We used a significance level of $p<0.05$.

The study was conducted in respect of the Principles of the Declaration of Helsinki, after approval of the protocol by the Hospital's Ethics Committee.

3. Results

3.1. Descriptives

Out of the 172 patients initially examined, complete data was obtained for 111, who met the eligibility criteria. The majority of our patients were diagnosed with RRMS (102, 91.9%), only nine patients (8.1%) being diagnosed with SPMS. Median EDSS score was 2 (SD 1.54), with values ranging from 1 to 6.5.

The mean age of our group was 41.7 years (SD 10.7), with a minimum of 21 and a maximum of 64 years old. We had a majority of female patients (65, 58.6% versus 46, 41.4% male).

A slight majority of patients were still working at the time of data collection (66, 59.5%), while the other 44 (40.5%) had already retired for medical reasons. Average age was higher in the retired group (46.4 years) as compared to employed patients (38,5 years). Mean age at retirement was 37 years (18-60, SD 9.61). The mean duration of professional activity in our group was 15.31 years (SD 10.215).

Median number of education years was 15 (4-24, SD 3.38). A majority of pwMS attended a higher form of education (67, 60.4%) while 34 patients (30.4%) attended high school and ten patients (9%) completed up to 8 years of school.

3.2. Evaluation of cognitive function

The IST scores had a median of 36 points in our group (min. 20, max. 40).

Comparison of IST scores in the retired versus employed pwMS revealed a significant difference ($p<.01$) between the two groups (**Table 1**). Retired patients showed a lower frequency of scores over 30 points and a higher frequency of scores under 26 (**figure 1A**).

In our group, participants who scored higher in the IST had a significantly higher educational status ($r=.242$, $p<.05$, data not shown). The Kruskal – Wallis Test showed that there was a significant difference between the three groups in IST scores: X^2 (2) = 7.638, p = .022 (**Figure 1B, Table 1**) with a mean rank IST score of 32.93 for the 'Low', 39.33 for 'Standard' and 53.37 for 'High' education group. Further analysis of the IST scores in the three education categories found no significant difference when comparing low versus standard education groups ($p>.05$), but significance was met when comparing the standard and high education groups ($p<.05$), and low versus high education groups ($p<.05$).

There was a higher frequency of IST scores above the maximum score (>40) in the employed group (X^2 (1) = 6.631, $p<.05$) (Table 1). Similarly, compared to the low and standard-educated participants, higher-educated patients had a higher frequency of IST scores above 40 points (X^2 (2) =6.855, p<.-05) (**Table 1**).

Table 1. IST median scores in subgroups defined by employment and educational status

IST scores by Retirement:		**Retired**	**Employed**	**p-value**
median +/- SD (min.-max.)		32.8 +/- 5.35 (20-40)	37 +/- 4.3 (26-40)	<.01
IST > 40 no (%)		8 (22.9)	27 (77.1)	<.05

Educational Status:	**Low**	**Standard**	**High**	**p-value**
median +/- SD (min.-max.)	32 +/- 3.8 (29-38)	34 +/- 5.42 (20-40)	37 +/- 4.62 (23-40)	<.05
IST > 40 no (%)	3 (8.6)	5 (14.3)	27 (77.1)	<.05

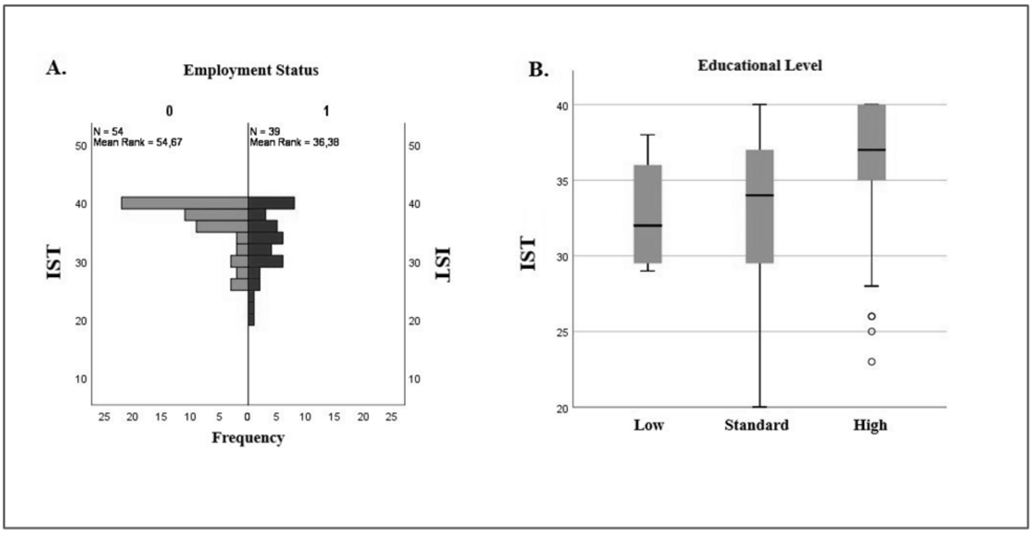

Figure 1. (A) IST scores in the retired (1) versus employed (0) group. **(B)** IST scores by educational level

3.3. Evaluation of physical function

Employed population was less disabled (as reflected by significantly lower EDSS scores) (p<.001) (**Table 2**), with the vast majority of this group (80.3%, data not shown) having an EDSS score of two or below two (showing minimal disability) (**Figure 2A**).

There was no significant difference when comparing EDSS in low versus standard-education participants. Highly educated participants had a significantly lower EDSS when compared to the other categories (**Table 2, Figure 2B**) with the following mean ranks: 76.85 for low, 66.73 for standard and 45.83 for highly educated participants (X^2 (2) =15.248, p<.001).

Intra-group analysis showed no significant correlation between EDSS or IST scores and education duration in the highly educated group. Within the retired group, higher EDSS scores correlated to an earlier retirement (r= -.283, p<.05).

Linear regression analysis revealed that a lower educational status could predict a higher disability score during the disease (p<.001, B= -0.43, 95% CI -0.607 to -0.264). Higher education also predicted higher IST scores (p<.05, B=0.256, CI 0.042-0.469).

Table 2. EDSS score in subgroups defined on employment and educational status

EDSS by:				
Retirement:		**Retired**	**Employed**	**p-value**
median +/- SD (min.-max.)		3.5 +/- 1.58 (1.5-6.5)	1.5 +/- 0.99 (1-6)	<.001
Educational Status:	**Low**	**Standard**	**High**	**p-value**
median +/- SD (min.-max.)	4 +/- 1.73 (1.5-6)	3 +/- 1.75 (1-6.5)	1.75 +/- 1.16 (1 - 6)	<.001

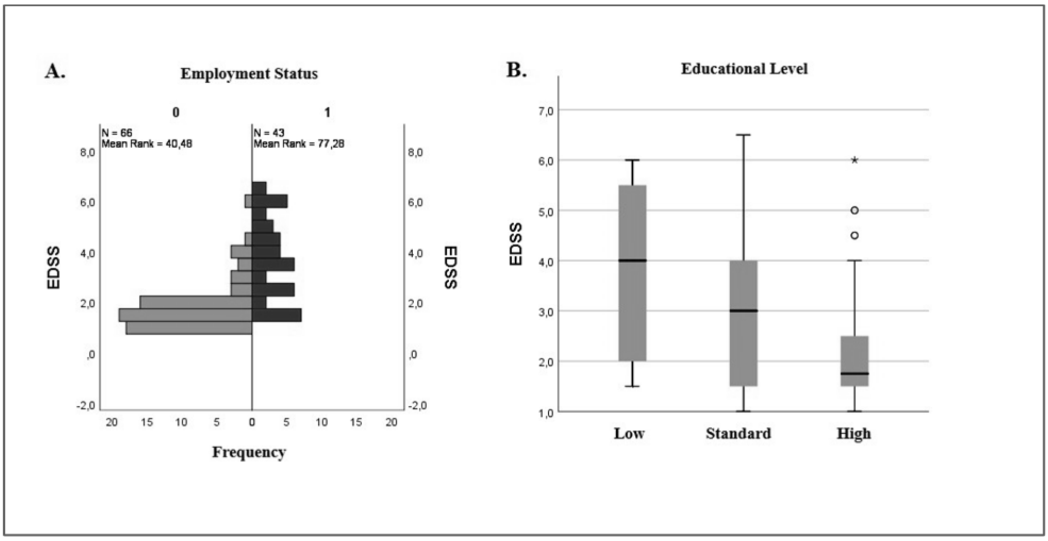

Figure 2. (A) EDSS in the retired (1) vs. employed (0) group. **(B)** EDSS by educational level

4. Discussion

The population included in our study is representative of an MS population, with a majority of female patients and a median EDSS score of 2. While most of our patients were working at the time of the study, a significant percentage (40.5%) were retired for medical reasons, with a mean age in the retired group of 46.4. Mean age at retirement was 37 years. In Romania, the legal age for retirement is 61 years for women and 65 years for men.

Patients who had never worked, self-employed, and agricultural workers were excluded from our study due to difficulties in assigning them a precise "medical retirement" moment. Employment status is a surrogate for "ability to work" and decreases reporting biases and confounding definitions of what "paid work" represents. Supporting our decision, a 6-year longitudinal cohort study in Scandinavia [15] found no significant differences between self-employed and employed pwMS regarding the need for a disability pension (although both groups had a significantly higher likelihood compared to matched controls).

Knowing the specifics of the disease, we can argue that early retirement is a natural consequence in pwMS. Chen et al. [16] analyzed the risk factors for leaving employment in pwMS. Initial data was collected in 2016 from 1240 patients who were then followed for ten years. Mean age at the time of retirement in this cohort was 48.6 years for a population similar in its characteristics to ours (regarding disease course, gender distribution, educational level). Most patients (78.7%) reported leaving work due to MS, but no further analyses were performed regarding which type of symptoms (physical, psychiatric or cognitive) was influential in this perspective. RRMS patients' employment status improved with time, correlated to an increased use of higher efficiency disease-modifying therapies (DMTs), while patients with progressive forms of MS had the same rate of leaving work [16]. At least two significant factors could explain the difference regarding the age at which our patients left work (over ten years of employment). Firstly, while the last five years brought improvements in the availability of highly active DMTs, both their usage and the moment when treatment escalation is happening need to be improved. Partly due to neurologists' hesitation, this issue can also be related to patients' availability to adhere to extensive monitoring and, in some cases, to more frequent appointments needed to administer highly active DMTs.

On the other hand, Romania is not a friendly environment for persons who have chronic diseases [17]. Awareness and inclusive policies that facilitate social and professional reintegration of people diagnosed with chronic illness are missing [17]. For pwMS living in our country, a medical pension may be the only available form of support (or the easiest attainable approach) as compared to a more difficult professional pursuit despite disability.

The median EDSS score in the retired population was 3.5 in our sample, translating to a fully ambulatory patient. Employment status significantly correlated to physical and cognitive status, but retirement at a relatively low level of disability appears to be a frequent occurrence in our group, suggesting that job retention depends on more than these two parameters. Raising awareness about the complex nature of disability that can occur during MS could have a substantial impact on the monitoring of patients' evolution and their quality of life.

Our study showed that higher-educated pwMS had better physical and cognitive function, with a stronger correlation for physical disability. Education status can predict cognitive and physical disability throughout the disease (as shown by the linear regression). A prospective study is necessary for a better understanding of both relationships.

The positive effect of education on physical disability could be explained by higher socioeconomic status achieved through education, which in turn gives access to more comprehensive tools with beneficial impact on physical function (as are physical therapy and sports). While equal medical treatment is granted to all in Romania, earlier access to therapy is achievable for patients with higher socioeconomic status, primarily through higher awareness and better use of medical tools (although these are accessible by standard health coverage).

Our results are consistent with other studies that addressed education's impact. Patti et all showed that quality of life is higher in educated and employed pwMS [18]. The author assumes that more educated patients benefited from better abilities to adapt and cope in response to MS.

People who spent more time studying are more likely to be employed for longer, making it difficult to analyze the two factors (education and employment) separately. Whether they act as protective factors, or whether they are endpoints to monitor and then influence through other interventions, they are essential aspects in the follow-up of pwMS.

Similar to the results reported by Conway et al. [9], we found no difference in cognitive evaluation scores between pwMS who only finished eight years of education and those who graduated high school. A significant difference was only found when compared to those who fit into the high-education group. As mentioned before, we have not assessed the extent of school dropout - we enclosed all persons who persuaded a college degree in the 'high' level of education. Since college and graduate degrees require more active effort, they are assumingly more appropriate indicators of intellectual capabilities than simple attendance, as would also be a longer type of higher education – in discordance to our data, as intra-group analysis in the high-education patients found no relationship between the number of education years and IST or EDSS.

Most of the patients in our study graduated high school and most fit the "high education" category as defined above. This is not representative for the educational status in our country. We assumed that the exclusion of stay-at-home/never worked persons has led to the exclusion of a group that would have fitted a lower academic level (in Romania, unemployment and low educational status are high, especially in rural areas). This assumption is not supported by our data, as post–hoc analysis revealed that this excluded category had a similar distribution regarding education, with representatives for all three levels of education. Chen et al. [16] showed that educated persons are usually more likely to report data, assumingly contributing to a timelier reaction regarding medical intervention. An increased resilience of more educated persons could also explain this aspect in our group. Low socioeconomic status is often associated with lower adherence and inconveniences in attending medical evaluations when asked.

The concept of cognitive reserve is widely used today when attempting to characterize individual discrepancies in brain pathology. In contrast to brain reserve (defined anatomically by brain volume), cognitive reserve is used for one's abilities and resources to approach situations and adapt to changes as are those induced by brain damage [19,20]. Cognitive reserve is a dynamic entity without consensus regarding its measurement [21]. Researchers inconsistently use an association of demographic, clinical, or imaging factors that correlate to the brain status in this field [21].

We used the IST to measure cognitive status as it assesses one's executive function and verbal abilities. In addition to other studies, we allowed patients to continue after reaching the target number of 10 elements per category. Our results showed that both highly educated and employed patients were more likely to generate over 40 elements in total. This strengthens available evidence that suggests that the test is a sensitive tool to assess cognition, even at high levels of functioning, due to its speed component [22].

We consider the IST a complex tool, valid for the screening and follow-up of cognitive decline in the heterogeneous population of pwMS. IST is easy to apply and could be used alone or as part of a more comprehensive battery of neuropsychological tests to address more cognitive domains.

The lack of a healthy control group is an important limitation to our study. Therefore, a longitudinal follow-up of this cohort is needed to better characterize the impact of education and employment on physical and cognitive disability.

5. Conclusions

Disability in pwMS patients is complex. While the physical component has in appearance the most significant impact on disease burden, factors like education and social support are important aspects that can affect not just one's ability to cope with living with MS but also influence its evolution.

Our study showed that worse cognitive (as shown by the IST) and physical status are expected in less educated patients and that better cognitive and physical performance as well as higher education correlate with employment retention.

IST is an easy-to-perform cognitive test and correlates with education, disability, and employment retention in MS. However, further validation is needed to include it in standard cognitive evaluations in MS.

Education level and cognition should be assessed in all MS patients along with physical disability as they could be associated with a higher level of disability and lower quality of life.

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