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Aging with multiple sclerosis: prevalence and profile of cognitive impairment

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Abstract

Background The increase in life expectancy of patients with multiple sclerosis (MS) requires a better knowledge of disease features in the older patients group.

Objective To describe the prevalence and profile of cognitive impairment (CI) in older patients with MS and perform a comparison with younger patients.

Methods Patients were consecutively recruited for 6 months. Cognitive performance was assessed through the Brief Repeatable Battery and the Stroop Test. CI was defined as impairment in ≥ 2 cognitive domains.

Results We identified 111 patients older than 55 years (mean age 59.7 years). The prevalence of CI was 77.4%, which was significantly higher than in younger patients (42.8%; $p < 0.01$). Information processing speed was the most impaired domain (68.8%), followed by verbal learning (49.5%), executive function (47.7%), and visuospatial learning (26.6%). We found no significant differences in the prevalence of impairment in the distinct cognitive domains between older and younger patients with CI. Depression and fatigue were not associated with increased CI among patients in the older age group ($p > 0.70$).

Conclusion There is a remarkably high frequency of CI in older patients with MS. The similar profile of CI between older and younger patients suggests that CI is mostly directly related to MS itself and not to comorbid age-related disorders.

Keywords Multiple sclerosis · Cognitive impairment · Aging · Epidemiology

Introduction

The prognosis of patients with multiple sclerosis (MS) has been improving during the last decades, due to the continuous development of disease-modifying therapies [1] leading to a rise in the average patient age [2]. Older patients with MS constitute a challenge to the clinician, because, on the one hand, the effects of aging on the course of the disease are still not satisfactory understood; on the other hand, older patients present comorbidities that have to be identified and differentiated from the symptoms secondary to the disease itself.

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Cognitive impairment (CI) is a well-established feature of MS [3], being identified in 40–60% of patients [4], with information processing speed representing the most affected domain [5]. However, the literature regarding CI in advanced ages is scarce. Besides, factors like depression and fatigue have to be taken in special consideration, as it is known that these are common symptoms in these older patients [6, 7], and may influence their cognitive performance [8, 9].

There are few studies in the literature regarding the interaction of aging and the risk of CI in MS, with heterogenous findings [10, 11]; moreover, there is little information concerning the neuropsychological profile of CI in older patients with MS, which may render it challenging to differentiate MS-related cognitive decline from other age-related conditions. Existing studies regarding the pattern of cognitive deficits of older patients with MS aimed to compare the neuropsychological profile of these patients with patients with AD or amnestic mild cognitive impairment (aMCI), showing a different cognitive profile between these entities [12, 13], although there might be some overlap [13]. However, these studies were based on relatively small samples, and none of them focused on the prevalence and determinants of CI in the older MS population.

The present study aims at describing the prevalence and pattern of CI in older patients with MS, and to compare these patients with a group of younger patients. We also explore the contribution of fatigue, depression, and late disease onset to the risk for CI in these older patients.

Methods

Study design and setting

The setting of the study was a nationwide Italian collaborative initiative, which was previously described in detail [11]. Briefly, patients with MS regularly followed in six Italian centers were consecutively recruited during a 6-month period. All the individuals underwent a standardized clinical assessment, including the Expanded Disability Status Scale (EDSS), therapeutic information, and collection of other demographic and clinical variables. A standardized neuropsychological evaluation was performed by well experienced neuropsychologists using the brief repeatable battery (BRB) [14] and the Stroop test [15]. The BRB is widely used and extensively validated for patients with MS, and includes the selective reminding test (SRT) to assess verbal learning, the 10/36 spatial recall test (SPART) to assess visuospatial learning, the paced auditory serial addition test (PASAT), and the symbol digit modalities test (SDMT) to measure complex attention and information processing speed and the word list generation (WLG) to explore verbal fluency. The

Stroop test was included to complement the BRB in order to provide an additional measure of complex attention and aspects of executive function.

Test failure was defined as a score below the 5th or above the 95th percentile, when appropriate, using age, sex, and education-adjusted Italian norms [16]. Impairment in each cognitive domain was defined as failure in a test assessing that domain, namely SRT for verbal learning, SPART for visuospatial learning, SDMT and PASAT for information processing speed, and WLG and the Stroop test for executive function. These theoretical cognitive domains were previously confirmed by principal component analysis in the whole sample [11]. CI was defined as impairment in at least two cognitive domains. The fatigue severity scale (FSS) [17] and the Montgomery and Asberg Depression Scale (MADRS) [18], while not part of the initial study protocol, were routinely used in several of the study centers and were also collected during the evaluation to assess fatigue and depression. In particular, the FSS was collected in 728/1040 and the MADRS in 356/1040 patients of the whole sample and, respectively, in 79/111 and 54/111 patients in the sub-sample of participants older than 55 years. For the purpose of this study, we selected the patients with 55 years or older, and compared them with the rest of the sample. This age cut-off was chosen considering it is when disorders affecting cognitive function start to become relevant and where epidemiological data on the prevalence of mild cognitive impairment (MCI) and dementia starts to become available [19, 20].

All the enrolled patients provided informed consent and the study was approved by the ethical committees of all recruiting institutions.

Statistical analysis

We compared the prevalence of CI, the neuropsychological profile, and the clinical and demographic and features between younger and older patients with MS and between impaired and preserved older patients with MS using the Student's t test for independent samples and the nonparametric Mann-Whitney test or χ^2 test where appropriate. The tests were two-sided, with a significance level of 0.05. To measure the association between the presence of CI in the older patient group and the different clinical and demographic variables (age, education, sex, late disease onset, disease duration, EDSS, clinical course, relapses in the previous year, FSS, MADR, treatment with disease-modifying drugs (DMDs)), we calculated crude odds ratio (OR) using logistic regression. In the older patient group, we also compared the clinical and demographic features between patients with a late-onset MS and those with a classical age at onset. Statistical analysis was performed using IBM SPSS Statistics version 24.0.

Results

We identified 111 patients with age ≥ 55 years from the total sample of 1040 adult patients with MS. The refusal rate in the largest study center (Florence) amounted to 14.5%; other study centers did not keep exact records of refusals; nevertheless, the feedback was that the vast majority of the patients agreed to participate.

The prevalence of CI steadily increased with age in this sample, from 28.7% in those aged 18–24 years to 91.7% in the group older than 65 years (Fig. 1). In the older patient group (age ≥ 55 years), the prevalence was 77.4%, while in the group of patients with less than 55 years, it was 42.8% ($p < 0.01$).

The main demographic and clinical characteristics of the two groups are listed in Table 1. The mean age of the older patients was 59.7 years, while it was 37.8 years in the group of younger patients ($p < 0.01$). The older patients had significantly lower education and a higher EDSS when compared with the younger patient group ($p < 0.01$). The distribution of disease subtypes was different between the groups, with increased frequency of progressive forms in the older patient group ($p < 0.01$). Sex distribution and frequency of current treatment with disease-modifying drugs were similar in both groups (Table 1). In the subset of patients with fatigue data ($n = 728/1040$), the mean FSS was 23.5 points (SD = 16.8) in the older patient group and 14.0 points (SD = 19.9) in the younger patient group ($p < 0.001$). The MADRS score (available in 356/1040 patients) was also significantly higher in older patients compared with the younger group (mean scores = 12.9; 9.8 and SD = 9.5; 8.7 respectively, $p = 0.02$).

When looking at the frequency of impairment by cognitive domain in the older patients with MS (age ≥ 55 years), impairment in information processing speed was the most common deficit (68.8%), followed by verbal learning (49.5%), executive function (47.7%), and visuospatial learning (26.6%). Among this older patient group, there was a trend for a higher EDSS (median 4.25 vs. 3.5) and age (mean 60.2 vs. 58.7 years) in cognitively impaired patients when compared with those without impairment, but with no significant differences (Table 2). There were also no significant differences between impaired and non-impaired patients concerning sex, disease subtype, education, or frequency of current treatment with disease-modifying drugs (Table 2). In the subset of the sample with fatigue assessment (79/111), impaired patients had a mean FSS score of 24.4 (SD = 19.9), compared with 19.0 (SD = 19.4) in those cognitively preserved ($p = 0.29$). There were also no significant differences in MADSRS scores ($p = 0.96$) in the subset with depression data (54/111), with mean score of 13.1 in cognitively impaired patients and 13.3 in cognitively preserved ones.

When comparing the cognitive profile of older and younger patients with CI ($n = 347$), we found no significant differences concerning impairment in verbal memory (69.0% vs. 64.0%; $p = 0.42$), visuospatial learning (38.6% vs. 43.6%; $p = 0.43$), executive functioning (80.0% vs. 82.5%; $p = 0.46$), or information processing speed (91.2% vs. 87.3%; $p = 0.37$; Table 3).

When analyzing the association between the different clinical and demographic variables and the presence of CI in patients using logistic regression in the older patient group, we did not find any significant association (Table 4) in the univariable regression, and therefore, no multivariable model was built.

Finally, we found that 24.7% of older patients in this sample presented with a late-onset MS (≥ 50 years [21]). When comparing this group with the group with a classic age of onset, we found no significant difference in the prevalence

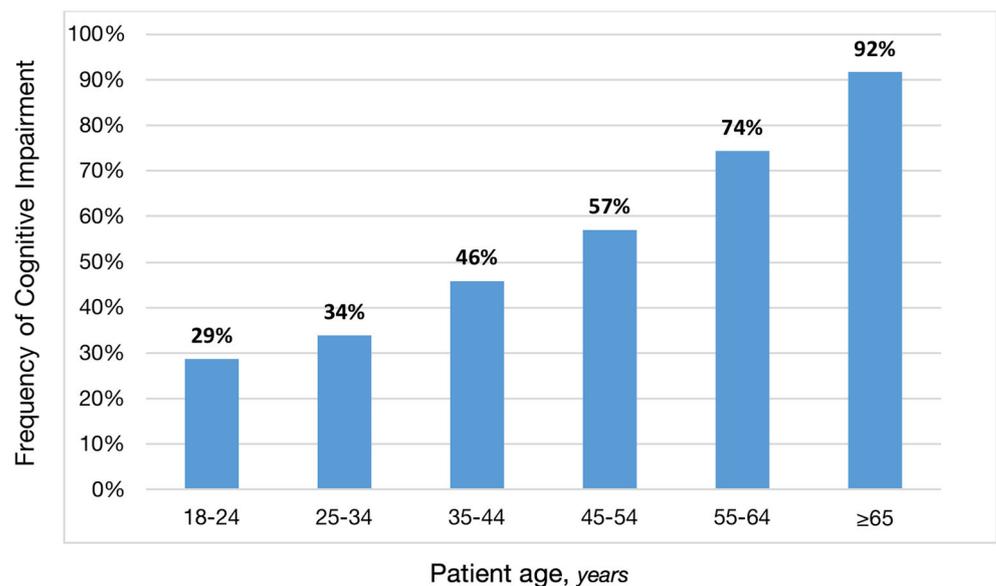**Fig. 1** Prevalence of cognitive impairment by age group

Table 1 Clinical and demographical characteristics of the study sample and prevalence of cognitive impairment

	Patients ≥ 55 years (n = 111)	Patients < 55 years (n = 929)	p value
Cognitive impairment (≥ 2 domains)	77.4%	42.8%	< 0.01
Sex (female), %	61.3%	68.5%	ns
Age, mean (SD) (years)	59.7 (4.0)	37.8 (9.0)	< 0.01
Disease subtype (%)			< 0.01
CIS	3.6%	17.5%	
RR	59.5%	74.6%	
SP	27.0%	4.7%	
PP	9.9%	3.1%	
Education, mean (SD) (years)	10.8 (4.7)	12.3 (3.5)	< 0.01
EDSS, median (IQR) (years)	3.5 (2.0; 5.25)	2.0 (1.5;3.5)	< 0.01
Treatment with DMDs (%)	54.1%	63.4%	ns

SD standard deviation, *IQR* interquartile range, *ns* non-significant ($p > 0.10$), *EDSS* expanded disability status scale, *DMDs* disease-modifying drugs, *CIS* clinically isolated syndrome, *RR* relapsing remitting, *SP* secondary progressive, *PP* primary progressive

of CI (76.7% vs. 79.1%; $p = 0.80$). There was also no significant difference regarding physical disability between these two groups (median EDSS 3.0 vs. 4.0 $p = 0.30$). When looking at the whole sample, there was an increased prevalence of CI in patients with a late-onset MS (74.2% vs. 45.2%; $p < 0,01$), but this was largely attributable to the older age of this group, as the association was not significant after adjusting for age in a logistic regression model (unadjusted OR = 3.5; adjusted OR = 1.2; $p = 0.63$).

Discussion

In this collaborative study, we assessed the cognitive performance of older patients with MS (≥ 55 years) using a neuropsychological battery specifically developed and validated for the disease. The study was not population-based; however,

due to the consecutive recruitment and the multicentric nature, our sample can provide a good representation of the global population of patients with MS who are 55 years or more and are referred to MS Clinics.

We identified a very high prevalence of CI in older patients with MS (77.4%), comparing to what is generally described in the literature for the overall population of these patients [4]. This is not unexpected, if we take into account that age is a main determinant of CI in patients with MS [11, 22], and that the large majority of the previously published studies was performed in younger patients [23, 24]. The comparison with younger patients showed a steady increase of the prevalence of CI by age group (Fig. 1), implying that many patients develop CI in a later stage of life. While there are some limitations when comparing the prevalence of CI, as defined in this study, with MCI and dementia in the general population, it is important to note that the prevalence of CI in this sample of

Table 2 Comparison of clinical and demographic characteristics between impaired and preserved older patients with multiple sclerosis (≥ 55 years)

	Patients with CI (n = 86)	Patients without CI (n = 25)	p value
Sex (female), %	60.6%	57.1%	ns
Age years, mean (SD) (years)	60.2 (4.2)	58.7 (3.4)	ns
Disease subtype (%)			
CIS	4.2%	4.8%	ns
RR	57.7%	66.7%	ns
SP	29.6%	23.8%	ns
PP	8.5%	4.8%	ns
Education, mean (SD) (years)	11.0 (4.8)	11.0 (4.1)	ns
EDSS, median (IQR) (years)	4.25 (1.5;5.25)	3.5 (2.0;5.0)	ns
Disease duration (years)	19.8 (12.6)	19.4 (11.0)	ns
Treatment with DMDs (%)	52.4%	54.9%	ns

CI cognitive impairment, *SD* standard deviation, *IQR* interquartile range, *ns* non-significant ($p > 0.11$), *CIS* clinically isolated syndrome, *RR* relapsing remitting, *SP* secondary progressive, *PP* primary progressive

Table 3 Comparison of neuropsychological profiles in cognitively impaired patients according to age. *CI* cognitive impairment, *ns* non-significant ($p > 0.43$).

	Patients ≥ 55 years with CI ($n = 86$)	Patients < 55 years with CI ($n = 347$)	*p* value
Verbal learning	69.0%	64.0%	ns
Visuospatial learning	38.6%	43.6%	ns
Information processing speed	91.2%	87.3%	ns
Executive function	80.0%	75.6%	ns
Impaired domains (*median*)	2.58	2.58	ns

MS patients is remarkably higher than the prevalence of MCI and dementia in the general European population [19, 20]. The older patient group compared with the younger one also presented higher physical disability levels, as well as higher average depression and fatigue scores.

The increased prevalence of CI in older patients with MS could raise the suspicion of a comorbid age-related neurodegenerative dementia, which would probably be the first diagnostic hypothesis in patients above 55 years without MS, and this hypothesis was suggested by some authors [10]. However, the cognitive profile of our sample is clearly compatible with MS-related CI, as shown by the prominent involvement of information processing speed, with the other domains being less affected. This is quite distinct from the typical cognitive profile of Alzheimer's disease (AD) and other neurodegenerative dementias, characterized by an early and

Table 4 Logistic regression analysis of the determinants of the prevalence of cognitive impairment in older patients with multiple sclerosis

	Univariate Regression	
	OR [95% CI]	*p* value
Age (*10 years*)	2.31 [0.63;8.47]	ns
Education (*years*)	0.99 [0.89;1.09]	ns
Sex (*female*)	1.00 [0.38;2.61]	ns
Late onset (*onset after 50 years*)	1.15 [0.38;3.55]	ns
Disease duration (*10 years*)	1.03 [0.69;1.52]	ns
EDSS (*2 points*)	1.03 [0.64;1.68]	ns
Clinical course		ns
RR vs. CIS	1.36 [0.14;13.18]	ns
RR vs. SP	1.43 [0.46;4.47]	ns
RR vs. PP	2.39 [0.27;21.02]	ns
Relapses in the previous year	1.03 [0.55;1.92]	ns
FSS (*5 points*)	1.08 [0.94;1.23]	ns
MADRS (*5 points*)	1.01 [0.69;1.49]	ns
Current treatment with DMDs	1.17 [0.45;3.03]	ns

OR odds ratio, *ns* non-significant ($p > 0.21$), *CI* confidence interval, *EDSS* Expanded Disability Status Scale, *CIS* clinically isolated syndrome, *RR* relapsing remitting, *SP* secondary progressive, *PP* primary progressive, *FSS* Fatigue Severity Scale, *MADRS* Montgomery and Asberg Depression Scale, *DMDs* disease-modifying drugs

prominent impairment of episodic memory [25]. This finding reinforces the results of previously performed studies. One study showed that memory impairment in older patients with MS is related to executive dysfunction, rather than a consolidation deficit as in AD [12], but the MS group was not evaluated with a battery of tests specifically developed for this population. A more recent study used a larger battery of tests, addressing the typically affected domains in both MS and AD, and compared groups of elderly patients with MS, AD, amnestic mild cognitive impairment (aMCI), and controls [13]. The results showed that patients with MS performed globally better than AD patients and pointed to an absence of retention deficit in MS, as well as to a possible overlap between MS and aMCI, illustrated by a comparable deficit in semantic fluency. An increased impairment in semantic fluency in older patients was also described in a population-based study [22] of patients with MS. However, we did not find any significant difference in this measure between younger and older patients in our sample (WLG impairment in 37.4% of older patients and 30.4% in younger patients, $p = 0.17$). At this regard, we can hypothesize that the prominent deficit in information processing speed in our sample had an impact also on the results of the WLG, which is a time-dependent test, thus obscuring differences in verbal fluency performance.

The differences in neuropsychological profile are useful to guide the differential diagnosis of CI in older patients with MS, although we cannot completely exclude an overlap between MS-related CI and degenerative dementia. It can also be challenging to differentiate CI secondary to MS from the one due to vascular dementia (VaD), which is very common in the elderly [26]. Cerebral small-vessel disease, most often associated with CI [27] in VaD, is characterized by lacunes and widespread ischemic white matter disease, which can resemble the white matter lesions seen in MS [28] and may contribute to cognitive decline by affecting information processing speed and executive functions [29]. Therefore, for the differential diagnosis, other clinical, laboratory, and imaging data are mandatory. This is particularly relevant taking into account that the incidence of vascular comorbidities such as diabetes, hypertension, and hyperlipidemia is rising within the MS population [30]. Biomarkers such as CSF tau and β-amyloid can also be important, as they would help to rule

out neurodegenerative dementia. One limitation of the present study is indeed the lack of assessment of the above factors.

The similar cognitive profile between older and younger MS patients suggests that CI in MS is probably a continuum process starting from the earliest stages of the disease and increasing over the disease course, although long-term, longitudinal studies starting from the early disease stages are the most appropriate approach to address this issue.

Finally, it is also interesting to note that the prevalence and profile of CI in patients with late-onset MS did not differ from those observed in patients with an age at onset < 55 years who grew old with MS, which suggests a preponderant, determinant effect of age per se, independent of disease duration. Therefore, in our sample, aging did confirm to represent a key determinant of poorer cognitive performance. Notably, in a previous study, also particularly young age at MS onset (< 18 years) was a relevant predictor of a poorer cognitive outcome in adulthood, possibly due to the interference of the pathological processes of the disease with ongoing brain growth and maturation in the pediatric population [31].

We did not find any significant association between CI and increased age and disability in this subsample of older patients. This is probably a consequence of the relative homogeneity of this subsample concerning these variables, with most patients presenting relatively high and homogeneous age and disability levels, since those were the main determinants of CI in the previous analysis of the whole sample [11]. Still, there was a trend for a higher age and EDSS in the group with CI. There was also no association between variables such as age, sex, disease subtype, disease duration, depression, and fatigue scores between the groups of cognitively impaired and preserved older patients.

Studying CI in older patients with MS can be particularly relevant since there are older patients with MS who express a phenotype predominantly represented by CI. In a study focusing on cognitive performance after three decades of disease, half of the patients presented CI, and one-third of these were only mildly physically disabled [32]. Therefore, in some patients, it could be important to perform a differential diagnosis between MS and other age-related disorders. Moreover, in patients with an established diagnosis of MS, CI may represent a marker of disease activity/progression, prompting changes of the therapeutic strategy. A limitation of the present study is the absence of data on the duration of current treatment, past therapeutic history, and the time of onset of CI and its relation to treatments. This precluded any meaningful conclusion on the relation of DMDs and cognition in this sample. DMDs may have, in principle, a positive effect on the patient cognitive outcome, decreasing ongoing inflammatory activity and accumulation of brain lesions, in a few cases reducing brain atrophy progression or acting on other key-pathogenic mechanisms of MS-related CI [33]. This effect has been implied in some clinical studies [34, 35] and, in future studies, it

would be interesting to specially explore the influence of past therapeutic history in the risk of CI in the population of older patients with MS.

Conclusions

Overall, the present study provides new insights on the topic of CI and aging with MS. These older patients have a substantially higher prevalence of CI, are more physically impaired, and present higher fatigue and depression scores. Moreover, they maintain the typical neuropsychological pattern of MS-related CI, which may help the differential diagnosis with other age-related cognitive diseases. Further research should more thoroughly characterize this emerging group of patients aging with MS, in order to pursue management strategies and therapeutic decision-making specifically tailored to the needs of this older population of patients.

Compliance with ethical standards All the enrolled patients provided informed consent and the study was approved by the ethical committees of all recruiting institutions.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that there is no conflict of interest.

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