Cognitive Decline in Older Multiple Sclerosis Patients

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Abstract

This narrative review focuses on several significant issues involving cognitive ageing and dementia in older adults with multiple sclerosis (PwMS): Are elderly MS patients more likely to experience cognitive impairment than older MS patients? Can PwMS get dementia as they age or other neurodegenerative conditions like Alzheimer's (AD) that could be hastened by MS? Exist any relevant biomarkers that might be used to identify the cause of cognitive deterioration in elderly PwMS? What are the neurological and molecular causes of neurodegeneration and cognitive ageing in MS? Although older PwMS may exhibit rapid cognitive deterioration, current research suggests that cognitive impairment in MS can be distinguished from that caused by other neurodegenerative illnesses. Although dementia is common in PwMS, its definition is still up for debate. Although further study is needed, it may be possible to identify disease processes associated with MS and other comorbidities like AD and vascular disease in older PwMS using cerebrospinal fluid and imaging biomarkers. In conclusion, one should be aware that cognitive deterioration might occur in older PwMS due to the coexistence of various underlying illnesses. Future fundamental and clinical research will need to take these complicated aspects into account to increase diagnostic precision and gain a better understanding of the pathophysiology at play.

Keywords: Multiple sclerosis • Cognitive aging • Cognitive decline • Neurodegeneration • Dementia

Introduction

The life expectancy of People With Multiple Sclerosis (PwMS) is growing, while it is still 6 years–10 years less than that of the general population. This is due to the development of disease-modifying medication, which has led to a decrease in demyelinating lesions and neurologic sequelae. With more accurate MS diagnoses, we are becoming more aware that MS can also appear after the age of 50 (late-onset MS), and that it may advance more quickly in older people. These variables together have led to an increase in elderly PwMS in the US and around the world. As a prevalent clinical symptom in PwMS, cognitive alterations associated with the MS disease process have long been acknowledged and continue to be of great study interest. It is still a difficult subject for both physicians and academics to determine what causes new cognitive symptoms or the progression of cognitive impairment in older PwMS. a case study An elderly woman who has had MS for many years and has a consistent cognitive impairment connected with it shows up at the clinic. She claims that she is having more difficulty remembering specifics of talks today, at the age of 71, and that she repeats queries quite a bit. Her doctor's appointments were missed as a result, and she was forced to start using a pill organiser to keep track of her prescription. Otherwise, there haven't been any neurological problems that have gotten worse or new. A recent standardised neuropsychological assessment found that she had deteriorated to below-average performance in verbal and non-verbal memory learning and retention, as well as category (animal) fluency, which represents a decline in her performance compared to five years earlier, along with previously identified impairments in attention, executive function, and processing speed. She questions whether she is exhibiting signs of dementia and if there is any medication that could improve her memory. Is there sufficient evidence in this case to recommend a different diagnosis, such as Alzheimer's Disease (AD), rather than ageing with MS? If so, what should be done next to confirm a possible diagnosis? Although a substantial body of research has shown that MS-related attention, processing speed, and episodic memory problems are common in PwMS and other cognitive traits have just recently been identified, it is yet unknown how these deficiencies may change or advance as PwMS age. In this review paper, we discuss the available data about the following issues: Are elderly MS patients more likely to experience cognitive impairment than older MS patients? Is it possible for older PwMS to acquire dementia or other neurodegenerative conditions like AD that could be hastened by MS? Exist any relevant biomarkers that might be used to identify the cause of cognitive deterioration in elderly PwMS? What are the neurological and molecular causes of neurodegeneration and cognitive ageing in MS? There are three primary parts where these issues are covered. Based on research utilising standardised neuropsychological measures, the first section of the paper discusses cognitive ageing in MS and the distinction in cognitive profiles between MS and other disorders. The topic of dementia in MS and its causes (such as underlying diseases and diagnostic tests) is covered in the second section. Studies examining the neurological and cellular basis of ageing and MS-related neurodegeneration are described in the third section. We then go back to talking about the vignette before wrapping up with succinct responses to the queries posed. To help clinicians and researchers who work with older PwMS understand ageing and cognitive changes and to spark ideas for future study, we intend to present a focused and critical narrative assessment of the current evidence.

Cognitive aging and MS

The prevalence of cognitive impairment is higher in older MS patients than in younger PwMS. According to one study, 42.8% of younger PwMS have cognitive impairment in two or more domains, compared to 77.4% of MS patients over the age of 55 [1]. According to a Norwegian study, 48% of participants met the criteria for cognitive impairment after 30 years of MS disease duration, which they defined as having an impaired score (1.5 standard deviations below the mean) in at least two of the four major cognitive domains (psychomotor speed, attention, learning/memory, and executive function). Given that older PwMS have a larger percentage of cognitive impairment, it is unclear whether this cognitive impairment is largely caused by the MS disease process, normal ageing in MS, or rapid decline brought on by both ageing and MS. Regardless of a prior MS diagnosis, the elderly are susceptible to other causes of cognitive declines, such as AD. The question of how cognition changes over time in PwMS has been the subject of several investigations. Previous studies revealed that MS sufferers experience age-related cognitive loss (especially in processing speed and language learning), however not at the same rate or degree as healthy control (HC) participants. This finding disproves the hypothesis that ageing and MS interact by showing that older PwMS do not experience accelerated cognitive loss. Bodling et al. (2009) found that a decrease in processing speed occurred in both MS (patients compared to HCs) and ageing (older compared to younger cohorts), but there was no interaction between these two factors. Their findings were based on 245 PwMS (18-74 years old) compared to 188 HC subjects on two measures of processing speed (the word reading and colour naming trials of the Stroop Test). However, compared to the Paced Auditory Serial Addition Test (PASAT) or the Symbol Digit Modalities Test (SDMT), which demand more executive control and put a greater strain on the frontal subcortical tracts, these measures of processing speed are less sensitive to the processing speed impairment typical of MS

[2,3]. The California Verbal Learning Test, Second Edition and the SDMT (for processing speed) were both used in a study by Roy et al (CVLT-II; for verbal learning and memory). The level of cognitive impairment in PwMS remained constant throughout the lifespan of our investigation. The scientists concluded that there was no indication of accelerated cognitive deterioration in elderly PwMS and that such rapid change might point to other illnesses other than ageing in MS. Although this should have theoretically increased the ability to measure differences between the groups due to increased cognitive reserve (i.e., the presence of protective factors against cognitive declines, such as higher levels of education) in the HC group, one cited limitation of this study was a higher education level in the HC group compared to the MS group. Based on these investigations, researchers had previously concluded that ageing does not accelerate the rate of cognitive change in PwMS [4]. In contrast to earlier research, more recent studies have demonstrated evidence of a relationship between ageing and MS in older PwMS when various study designs were taken into account and more thorough metrics were analysed. Cognitive abilities in late-onset MS (LOMS; the age of symptom onset>40 years; mean 48.4) and adult-onset MS were compared by Pagnotti et al. in 2021. (AOMS; the age of symptom onset up to 40 years; mean 28.8). After adjusting for disease duration and co-occurring cardiac disorders, LOMS patients showed more reduced age-adjusted working memory and visual memory scores than AOMS patients. The authors proposed that age-related brain alterations in older PwMS may exacerbate the inflammatory changes associated with MS. Together, these changes may overwhelm the available cognitive reserve, causing a quicker rate of cognitive decline in LOMS patients. For AOMS versus LOMS, this study used a somewhat different cognitive battery. Although it is doubtful that this had a significant impact on the outcomes, it would be crucial to repeat these outcomes with identical batteries in both groups. Another study included 50 HC participants, 84 PwMS (including 30 young AOMS, 30 older AOMS, and 24 older LOMS), and (25 young, 25 older). The authors discovered an interaction impact between age and MS on attention, executive function, and processing speed performance, but not on measures of episodic memory by contrasting young versus older subgroups across AOMS and HCs. Additionally, Tremblay et al. discovered that higher processing speed and working memory impairments were brought on by longer disease duration [5]. Notably, this study was one of the first to incorporate psychosocial factors that can obscure the influence of MS on ageing, such as anxiety, sadness, fatigue, and medical comorbidities. Despite the numerous benefits of the aforementioned two studies, it is unclear from the definition of symptom onset whether cognitive symptoms, which have gained more recognition recently, were included in the initial presentation that resulted in an MS diagnosis. If so, the results may have been skewed if these patients were unequally distributed between AOMS and LOMS. Several further research has suggested that older age contributes to cognitive abnormalities in MS. Regardless of the clinical subtypes of MS, Ruano et al. (2017) discovered that greater age was related to the existence of cognitive impairment (i.e., impaired scores in at least two cognitive domains). When controlling for variables including physical activity and years since diagnosis, Baird et al. (2019) discovered that processing speed was poorer in older PwMS, whereas visuospatial learning and memory were worse in both older and middle-aged PwMS. Processing speed was shown to be hindered in older PwMS in comparison to similarly aged HCs, a finding that is well-established in young PwMS, according to Jakimovski et al. (2019) and Roth et al. (2018). Even though Roy et al. (2017) concluded that MS did not hasten age-related cognitive changes, a closer look at their data revealed that CVLT-II showed a marginally significant trend (p=0.02, exceeding their threshold of 0.01), indicating that verbal learning declines more quickly in MS as people get older. Although the majority of the evidence so far is based on younger rather than older PwMS, one should keep in mind when examining this research that cognitive reserve may also affect the trajectory of cognitive ageing in MS. The concept of cognitive reserve has been developed in the literature on ageing and dementia [6]. It is used to explain some of the individual differences in cognitive performance and is believed to account for the relationship between several protective factors, such as education, intellectual and recreational activity levels, employment status, vocabulary, and others, and a decreased incidence and prevalence of cognitive decline. Higher cognitive reserve (using premorbid IQ, education, and cognitive leisure activities) in MS is linked with better verbal memory and verbal fluency performance cross-sectionally after correcting for brain atrophy, but not with attention or processing speed [7]. However, the degree of brain volume and lesions rather than cognitive reserve explained the cognitive change over a two-year follow-up. In contrast, greater age and worsening cortical atrophy, rather than the cognitive reserve, were predictive of cognitive decline over 1.6 years, according to another study that examined the relationship between cognitive reserve and cortical atrophy. According to this research, having a higher cognitive reserve may be beneficial since it allows for a better adaptation to cognitive changes that come with ageing, but the ability to adapt is ultimately surpassed by the disease's course. One study discovered that lesser cognitive reserve (i.e., education, vocabulary) was predictive of more cognitive decline in processing speed assessments at the 5-year follow-up, in contrast to the studies above that revealed cognitive reserve alone was not predictive of ensuing cognitive decline. However, unlike the previous research, this one did not include volumetric measurements that might have affected the results. It is yet unknown how cognitive reserve, or older PwMS in general, predicts cognitive deterioration in older PwMS with LOMS. By providing an answer to this question, we may be able to identify PwMS who are at risk for cognitive decline and determine whether adding intellectual enrichment programmes or other therapies that aim to improve cognitive reserve can assist prevent cognitive decline [8]. The research was done to compare cognitive impairment associated with older PwMS as opposed to those with amnestic mild cognitive impairment (aMCI), a prodromal stage of AD, or AD the most common neurodegenerative disease in the older to address more specifically how cognitive changes in older PwMS may differ from that in older adults with other neurodegenerative conditions. Such studies can be very instructive for clinical care and analysis in older PwMS-related research. Patients with progressive MS performed worse than AD patients in the first study of its kind by Filley et al. (1989) in terms of attention and processing speed, but better than AD patients in terms of learning, memory, and linguistic skills. In a more recent study, Roy et al. (2018) compared older PwMS with AD, aMCI, and HCs (n=20 in each group) who were divided into cognitively impaired and unimpaired subgroups. They discovered that the impaired MS subgroup had decreased category fluency equivalent to aMCI despite the absence of confirmation biomarkers for AD diagnosis, but did not exhibit as much quick forgetting (measured by retention of verbal memory) as the AD and aMCI groups. They concluded that, while MS and aMCI had some cognitive characteristics, MS was fundamentally different from AD. However, Jakimovski et al. (2019), who also discovered impaired category fluency in older PwMS compared to similarly aged HCs, raise the question of whether impaired category fluency may signify growing cognitive impairment due to different aetiologies. The distinction between cognitive characteristics in older MS and aMCI patients is supported by several studies. Older PwMS perform worse on measures of processing speed, better on measures of cued memory, picture naming, and executive function (after controlling for processing speed), and have relatively preserved semantic autobiographical memory and memory storage (recognition) according to a summary of studies comparing aMCI patients [9,10]. Overall, these investigations suggest that older PwMS should be concerned about AD-related diseases if specific cognitive tests are affected.

The high prevalence of several significant comorbidities of cognitive decline in MS may be a factor in the observed cognitive deficits, accelerated cognitive decline, and higher mortality, particularly in older PwMS. Particularly, the prevalence of vascular comorbidities (hypertension, hyperlipidemia, ischemic heart disease, etc.) is higher in MS patients compared to the general population, and it rises with age. Future studies will need to take into account the possible effects of these MS-related and age-related comorbidities on cognitive ageing in MS since very few studies on cognitive function in older PwMS have taken these comorbidities into account yet. In conclusion, recent studies suggest that older PwMS show a more rapid decline in multiple cognitive domains, including those typically seen in MS (e.g., attention, executive function, working memory, processing speed, visual memory), as well as in domains less typically impaired in MS. This is despite heterogeneity in the samples and methodologies (e.g., category fluency). Additionally, there is evidence that, particularly in measures of semantic memory and memory storage/retention, the pattern of cognitive impairment in older PwMS can be separated from that of aMCI and AD patients. It is yet unclear how cognitive reserve affects this deterioration. In the future, study designs taking into account disease duration and clinical subtypes (such as clinically isolated syndrome, relapsing-remitting MS, primary and secondary progressive MS), as well as age-related and MS-related confounding factors (such as fatigue, cognitive reserve, depression, and vascular comorbidities), will be necessary to clarify this area of research. The results of cross-sectional investigations should be replicated and expanded upon by prospective longitudinal studies, which are lacking. Creating age-adjusted normative data for cognitive performance in PwMS as a benchmark to identify abnormal cognitive ageing in older PwMS, could also help therapeutic care.

Conclusion

Recent studies have better accounted for confounding MS-related symptoms (fatigue, disease duration, depression, etc.) and comorbidities including cardiac disease, and current research suggests that ageing interacts with the MS disease process. Cross-sectional research indicates that, except for "cortical MS," the cognitive profiles of ageing and dementia brought on by MS in older persons can be separated from those of other neurodegenerative disorders.

Future Directions

More research is needed to better understand how these mechanisms affect the cognitive decline in elderly PwMS because they are surviving longer than ever before. Here, several potential directions are offered and compiled. Study designs will need to take potential confounding factors, disease duration, and clinical MS subtypes into account to more accurately describe age-related vs MS-related cognitive alterations and their potential interaction (for example, accelerated ageing in MS). To explore how cognitive changes develop as younger PwMS age, prospective longitudinal studies are required to characterise the cognitive trajectory and replicate findings from cross-sectional investigations. Establishing age-adjusted normative data for cognitive function in PwMS can help doctors identify early signs of aberrant cognitive ageing and consider alternative treatments in older PwMS. In addition to the investigation of biomarkers and neuropathological correlates to establish the relationships between clinical presentation, diagnostic tests, and pathology, more systematic research is required to better define dementia and its cognitive/functional trajectory in older PwMS. Future studies should look into how various patterns or progressions of cognitive impairment may be influenced by MS and other coexisting age-related illnesses (such as AD, Lewy body disease, and cerebrovascular disease). The use of multimodal techniques in this study will help to clarify the pathophysiology of cognitive ageing and neurodegeneration in MS at the cellular, systemic, and behavioural levels. By more accurately tracking the progression of concomitant disorders, creating tailored medicines, and keeping track of therapy responses, the anticipated results will have a considerable clinical influence on the care of elderly PwMS.

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