

Multiple Sclerosis in People Over Age 55

The average age of people with MS is increasing, but knowledge of the disease in people over age 55 remains sparse.

By Abedallah A. K. Balusha, MD and Sarah A. Morrow, MD, MS, FRCPC, FAAN



Multiple sclerosis (MS) is a chronic inflammatory disease that affects the central nervous system (CNS) and is characterized by inflammation and demyelination resulting in neurologic

disability that may be irreversible. It is considered the most common cause of non-traumatic neurologic disability in adults.¹ Historically, MS was recognized as a disease of young people as the typical onset is between age 20 to 40 years.² The life expectancy of the general population, however, is increasing. Additionally, advances in MS treatment have led to an increase in the average age of persons with MS.³ Thus, MS can no longer be considered a disease of earlier adulthood only because clinicians will be treating people with MS into their later decades of life. Simultaneous management of aging and MS is among the current unmet needs in MS care, considering the unclear phenotypes, disease course, associated comorbidities, aging of the immune system (immunosenescence), MRI characteristics, response to disease-modifying therapies (DMTs), and disease progression. In this review, we address several issues pertinent to the care of people with MS in a person's mid50s and beyond, discussing the epidemiology of MS in this population, immunosenescence, use of DMTs, and, finally, cognitive impairment.

Epidemiology of MS After Age 55

Multiple sclerosis affects persons of all ages. Age is a predictor of MS phenotypes and onset of relapsing MS (RMS) between age 20 to 40 years accounts for 80% of cases. Secondary progressive MS (SPMS) is considered the long-term outcome of RMS, but more than 30% of people with MS continue to have RMS at an advanced age.⁴ Only 3.4% of people with MS are diagnosed with RMS after age 50, considered late-onset MS, and only 1% are diagnosed after the age 60, considered very late-onset MS.²

In contrast, the primary progressive MS (PPMS) phenotype tends to present after age 45 and accounts for 10% to 15% of cases. PPMS is characterized by a slow neurologic decline

from onset.⁵ Yet, the overall demographics of people with MS are changing to include people in their mid50s and later. For example, in Manitoba, Canada, the reported prevalence of MS has increased from 32.6 per 100,000 in 1984 to 226 per 100,000 in 2006, with evidence of increased age of peak prevalence from 35 to 39 years to 55 to 59 years.⁶ Similarly, in Italy, 18% of people with MS are age 65 or more.⁷ Thus, the care of people age 55 and more is becoming part of routine practice in MS clinics. Whether people with MS who first present later in life have a different phenotype is not yet well studied.



CLINICAL GEMS

The prevalence of MS in people over age 55 is increasing, with increasing comorbidities adding challenges to their care.

Immunosenescence

Aging is well known to be associated with progressive loss of innate and adaptive immune system proficiency and an adequate immune response (immunosenescence). These changes have many implications for people with MS.⁸ It has been suggested that there are 2 parallel inflammatory processes during the course of MS that manifest as the relapsing and progressive MS phenotypes. In simple terms, the first is invasion of the brain by T and B lymphocytes through a blood-brain barrier damaged by inflammation, presenting as clinical relapses and active demyelination. The second is a slow accumulation of B and T cells in the meninges without major blood-brain-barrier breakdown, forming aggregate or lymphoid follicles, which cause a slow inflammatory process and neurodegeneration, resulting in a progressive phenotype. These latter changes may present early in the course of MS but become more predominant at late stages.⁹

In the early stages of MS, typically occurring at age 20 to 40 years, the immune system is more functional, with repair capacity that is more effective in healing the inflammatory damage. With aging, the immune system repair capacity decreases, and axonal degeneration, iron deposition, and oxi-

ductive stress occur, leading to decreased natural brain reserve. This gradual decrease in healing and brain reserve might partly explain the progression of MS seen with aging.¹⁰ The difference between the immune response in the early stage of RMS compared with progressive MS may also explain why evidence of reduced disability and disease progression has not been shown for most DMTs, based on probable different mechanisms of disease activity for relapse vs progression.¹¹



CLINICAL GEMS

Immune system aging plays a key role in MS progression, and disease-modifying treatment efficacy may be reduced by immune system changes and aging.

It also has been suggested that aging is associated with low-grade inflammatory processes resulting from previous viral infections (eg, cytomegalovirus or Epstein-Barr virus) over the lifespan. This phenomenon is called *inflamm-aging* and results in accumulation of senescent immune cells that are no longer able to play a role in the tissue repair process. Senescent immune cells are thought instead to produce a continuous slow inflammatory process and secrete proinflammatory growth factors, cytokines, and antibodies. This shift to a proinflammatory state would also contribute to further damage rather than tissue repair and, hence, gradual functional decline. Based on this observation, antiaging strategies might be a future focus in that decreasing inflammaging without affecting normal physiologic inflammatory processes could thereby increase survival and slow disability progression.¹²

Disease-Modifying Therapy

Our knowledge regarding DMTs in people over age 55 with MS, regardless of the type of MS, is still minimal and further studies are warranted to better understand when these medications should be discontinued. To date, few studies have assessed the efficacy and safety of DMTs in people over age 55, with only a few clinical trials including this population. Yet, the number of persons with MS in this age group is increasing, and progressive MS is more common in those over age 65.³ Among the few studies to include people over age 55 was a retrospective study assessing the efficacy of interferon β -1b in people with MS over age 50; however, the study did not demonstrate a significant decrease in disability in those over age 50 on follow-up.¹³ A subgroup analysis of a double-blind randomized placebo-controlled trial assessing the efficacy of fingolimod compared with placebo in people with MS more than age 40 did not show a significant difference in the annualized relapse rate (ARR).¹⁴ Overall, our knowledge regarding the efficacy and safety of DMTs in people with MS more than age 55 is limited, and further studies are needed.

There are now 2 DMTs approved to treat progressive MS. Ocrelizumab is approved for PPMS,¹⁵ although people over age 55 were excluded from the phase 3 trial of ocrelizumab. Siponimod is approved for SPMS, although the upper age limit for inclusion in clinical trials of siponimod was 60.¹⁶ An open-label study of the efficacy and safety of ocrelizumab in persons with progressive MS inclusive of people up to age 65 years is ongoing.^a The reasons for excluding people with MS who are over age 55 from most clinical trials are not well addressed but might be due to a multitude of factors, including previous underestimation of MS prevalence in this population, the decrease in inflammation with age and immunosenescence in MS, associated comorbidities that might affect planned study outcomes, and concern about the safety and efficacy of DMTs in this population with other comorbidities. In a meta-analysis of 45 clinical trials age-related risk of infection and neoplasms associated with DMTs was evaluated. By comparing DMT mechanisms of action, the analysis found increased risk of neoplasms with increasing age while on immunodepleting DMTs, with no clear evidence of an age-related increase in infection risk.¹⁷ In contrast, another study showed evidence infection risk and infection-related mortality increased with age in individuals who were being treated with immunomodulatory and immunosuppressive MS agents, which might reflect again the interaction between Immunosenescence and DMT use.⁸



CLINICAL GEMS

With increasing age, people with MS using immunomodulating therapies should be screened and observed for malignancies and infections, because occurrence increases with age.

Cognitive Impairment

Cognitive impairment (CI) is common in MS, with a prevalence of 40% to 65%. CI can occur at any stage of MS, starting at radiologically isolated syndrome (RIS), but onset of CI has been noted at all stages of MS. CI in MS can affect attention, episodic memory, information processing speed, and executive functions. CI can be extremely debilitating for people with MS, with substantial negative effects on activities of daily living.¹⁸

The characteristics and type of CI may differ among MS phenotypes. A cross-sectional study used a large battery of neuropsychologic tests to assess affected domains of cognition in people with PPMS vs RMS. Those with PPMS had more impairment in information processing speed, attention, executive function, and working and episodic memory, whereas those with RMS group had impairment predominantly in information processing speed and working memory.¹⁹

In a 10-year longitudinal study of cognitive function in persons with MS (n=50), prevalence of CI increased from 26% to

a An Open-Label, Single-Arm 4-Year Study to Evaluate Effectiveness and Safety of Ocrelizumab Treatment in Patients With Progressive Multiple Sclerosis (NCT03523858)



CLINICAL GEMS

Early and routine screening for cognitive impairment is recommended as a part of MS management.

49% during the first 4 years. By the end of the study, 56% of participants had mild-to-moderate CI, supporting the concept that MS-related progression and prevalence of CI increases as the duration of MS increases.²⁰

CI in MS and the relationship of CI in MS to aging and physical disability were investigated in a large study of prevalence and phenotypes of CI in people with MS (n=1,040) with different phenotypes and stages of MS. Increasing age and disease duration were found to be the main determinants of CI. Additionally, people with either PPMS or SPMS had twice the risk of CI compared with those who had RMS or clinically isolated syndrome.²¹

Classically, MS-related CI does not present with aphasia, apraxia, or anomia and thus is a distinct phenotype from other dementias. Among the challenges of diagnosing CI in people over age 55 with MS is whether the cognitive dysfunction being assessed is part of the Alzheimer disease (AD) spectrum, including prodromal amnesic mild cognitive impairment (AMCI), or is MS-related CI alone. A study used neuropsychologic measures used in diagnosing AD (ie, the Logical Memory subtest of the Wechsler Memory Scale for verbal episodic memory, semantic fluency for verbal fluency, Boston Naming Test for confrontation naming, and the sorting test from the Delis Kaplan Executive Function System (D-KEFS) for executive function) and found distinct cognitive profiles that differed between MS and AD and AMCI, suggesting these are distinct from each other, with only some overlap in semantic fluency deficiency among those with MS and AMCI.²²



CLINICAL GEMS

Cognitive impairment in MS has specific characteristics that can be distinguished from other cognitive disorders with neuropsychologic testing.

Conclusion

MS today is no longer only a disease of early adulthood, regardless of age of onset and MS phenotype. The prevalence of people with MS over age 55 is increasing; their unique presentations should not be overlooked. It seems that immune system aging plays a role in the course of MS. As we age, the immune system does as well, resulting in an immune system with less ability to adequately respond and repair. This increased prevalence of dysregulated immune responses may explain some characteristics of that change with age. The

available data regarding DMTs in people with MS over age 55 remains sparse because most clinical trials excluded this population. Further studies in this age group are warranted.

Finally, other factors in this age group must be considered, such as associated comorbidities, aging of the immune system (immunosenescence), response to DMTs, disease progression, and cognitive impairment, when addressing the treatment and ongoing care of persons with MS over age 55. ■

1. Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. *Lancet*. 2017;389(10076):1336-1346.
2. Roohani P, Emiru T, Carpenter A, et al. Late onset multiple sclerosis: Is it really late onset? *Mult Scler Relat Disord*. 2014;3(4):444-449.
3. Vaughn CB, Jakimovski D, Kavak KS, et al. Epidemiology and treatment of multiple sclerosis in elderly populations. *Nat Rev Neurol*. 2019;15(6):329-342.
4. Tutuncu M, Tang J, Zeid NA, et al. Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. *Mult Scler J*. 2013;19(2):188-198.
5. Antel J, Antel S, Caramanos Z, Arnold DL, Kuhlmann T. Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity? *Acta Neuropathol*. 2012;123(5):627-638.
6. Marrie RA, Yu N, Blanchard J, Leung S, Elliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. [published correction appears in *Neurology*. 2011 Sep 13;77(11):1105]. *Neurology*. 2010;74(6):465-471.
7. Solaro C, Ponzio M, Moran E, et al. The changing face of multiple sclerosis: prevalence and incidence in an aging population. *Mult Scler J*. 2015;21(10):1244-1250.
8. Grebeniucova E, Berger JR. Immunosenescence: the role of aging in the predisposition to neuro-infectious complications arising from the treatment of multiple sclerosis. *Curr Neurol Neurosci Rep*. 2017;17(8):61.
9. Lassmann H. Pathogenic mechanisms associated with different clinical courses of multiple sclerosis. *Front Immunol*. 2019;9:3116.
10. Peterson JW, Trapp BD. Neuropathobiology of multiple sclerosis. *Neurol Clin*. 2005;23(1):107-vii.
11. Hemmer B, Kerschensetter M, Korn T. Role of the innate and adaptive immune responses in the course of multiple sclerosis. *Lancet Neurol*. 2015;14(4):406-419.
12. Cevenini E, Monti D, Franceschi C. Inflamm-aging. *Curr Opin Clin Nutr Metab Care*. 2013;16(1):14-20.
13. Shirani A, Zhao Y, Petkau J, et al. Multiple sclerosis in older adults: the clinical profile and impact of interferon beta treatment. *BioMed Res Int*. 2015;2015:451912. doi:10.1155/2015/451912.
14. Devonshire V, Haydova E, Radue EW, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. [published correction appears in *Lancet Neurol*. 2012 Aug;11(8):658]. *Lancet Neurol*. 2012;11(5):420-428. doi:10.1016/S1474-4422(12)70056-X.
15. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209-220.
16. FDA approves new oral drug to treat multiple sclerosis. News release. FDA. March 24, 2020. Accessed January 6, 2021. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-oral-drug-treat-multiple-sclerosis>
17. Prosperini L, Haggag S, Tortorella C, Galgani S, Gasperini C. Age-related adverse events of disease-modifying treatments for multiple sclerosis: a meta-regression. *Mult Scler J*. 2020;135245852096477. doi:10.1177/1352458520964778.
18. Jongen PJ, Ter Horst AT, Brands AM. Cognitive impairment in multiple sclerosis. *Minerva Med*. 2012;103(2):73-96.
19. Ruet A, Deloire M, Charré-Morin J, Hamel D, Brochet B. Cognitive impairment differs between primary progressive and relapsing-remitting MS. *Neurology*. 2013;80(16):1501-1508.
20. Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. *Arch Neurol*. 2001;58(10):1602-1606.
21. Ruano L, Portaccio E, Goretti B, et al. Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. *Mult Scler*. 2017;23(9):1258-1267.
22. Roy S, Drake A, Snyder S, et al. Preliminary investigation of cognitive function in aged multiple sclerosis patients: challenges in detecting comorbid Alzheimer's disease. *Mult Scler Relat Disord*. 2018;22:52-56.

Abedallah A. K. Balusha, MD

Department of Clinical Neurological Sciences
Western University
Department of Cognitive Neurology, Parkwood Institute
London, ON Canada

Sarah A. Morrow, MD, MS, FRCPC, FAAN

Department of Clinical Neurological Sciences
Western University
Department of Cognitive Neurology, Parkwood Institute
London, ON Canada

Disclosures

AAKB and SAM report no disclosures