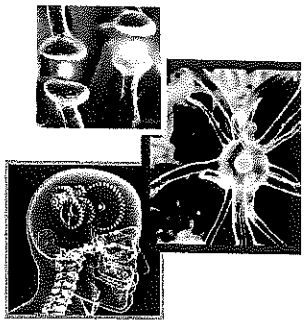
REVIEW

Neurodegenerative Disease Manageme



Aging with multiple sclerosis: cognitive, emotional and neuropathological considerations

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PRACTICE POINTS

- Providers should pay special attention to patient's social support and should encourage patients to remain active socially.
- Keep in mind that patients and caregivers will often disagree about the presence of cognitive symptoms, especially female patients and those with a long disease duration.
- While rates of cognitive decline are variable, they seem to be relatively slow in multiple sclerosis (MS) and comparable to that seen in normal aging. Processing speed, attention and memory seem to be particularly affected in older MS patients.
- Detailed evaluation is necessary if older MS patients show poor recognition memory with poor recall, as this might suggest an amnestic mild cognitive impairment process.
- There are mixed results as to whether older patients have a higher prevalence of depression, although they have been shown to have more MS-related helplessness.
- MS patients and aging individuals often show gradual and diffuse neural changes including atrophy and lesions, which appear to cause a dedifferentiation in functional connectivity. MS patients appear to have a higher rate of atrophy, although with age they seem to show a normalization of inflammatory and neurodegenerative processes.

SUMMARY Although individuals aging with multiple sclerosis (MS) can experience a compounding of their symptoms, in some circumstances they become more adept at coping with aging-related changes. Fortunately, individuals aging with MS often adjust well to aging, particularly if they have sufficient social support. They also do not appear to show accelerated rates of cognitive decline, and rates of some neuropathological changes have been shown to normalize compared with those seen in normal aging. Results are mixed as to whether older MS patients have higher rates of depression.

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Multiple sclerosis (MS) is a chronic, unpredictable neurological illness that is usually diagnosed in an individual's 20s or 30s and typically shortens patients' lives by 5–10 years [1]. Thus, 50% of patients live over 30 years after diagnosis [2]. The percentage of MS patients older than 65 years is estimated to be approximately 9%; therefore there are approximately 225–350,000 patients older than 65 years living with MS worldwide [3]. However, aging with MS remains understudied, potentially owing to the complicated nature of differentiating aging-related and MS-related processes. Indeed, many symptoms of MS are also seen in aging (e.g., pain, fatigue, depression, cognitive changes, visual disturbances and problems with mobility), so it is difficult to differentiate normal age-related changes from MS-related changes. Furthermore, normal aging and MS also share some neuropathological processes (e.g., demyelination and gray matter [GM] atrophy) [4]. Lastly, it is difficult to disentangle the unique effects of age and disease duration.

On the one hand, aging with MS can be seen as two detrimental processes exacerbating the effects of the other. For instance, some investigators have proposed that patients with MS age at an accelerated rate [5,6] and many physical symptoms such as fatigue, incontinence, weakness, cognitive impairment and visual change can be worsened by the reduced muscle strength and cardiopulmonary reserve seen in aging [7]. Furthermore, older patients with MS potentially face both the stigma of disability and of aging, and these can be internalized [7]. By contrast, others have suggested a more optimistic picture of aging with MS. Some studies have shown lower rates of depression in older MS patients (although findings are mixed), as well as increased predictability of disease and more successful coping [8–11].

In general, the clinical phenotype and course of MS has been found to be 'age-dependent' [12]. That is, relapsing–remitting (RR) and secondary progressive (SP) MS can be viewed as different time points of the same disease process as opposed to distinct disease processes [12]. However, age of MS onset has been shown to affect disability development. A recent study found that age independently affected disability development, primarily by increasing the probability and shortening the latency of secondary progressive onset [13]. In other words, individuals with later age of onset of RR disease had a higher risk of reaching advanced disability. This effect was independent of disease duration, but was secondary to increased risk of conversion to SP MS. There have been several excellent reviews written on MS and aging, most recently by Finlayson in 2009 [14]. The current review will mostly highlight research conducted since 2009, and in areas with relatively few recent studies, also earlier research not cited in Finlayson's review. This review will focus on perceptions of those aging with MS, cognitive/psychological factors and neuropathological considerations. In general, we aim to describe the factors that make aging particularly difficult for patients with MS, and those factors contributing to healthy aging with MS.

Experiences/perceptions of patients

Much useful information can be gained from qualitative, interview-based studies asking MS patients and their caregivers directly about their experience with aging. One recent study conducted semistructured interviews on 18 patients with MS to examine patients' perspectives on aging and their health and lifestyle habits (aged 56–80 years, 17% RR and 71% SP) [15]. When responses were coded and analyzed for themes, two levels of factors were found that influenced healthy aging in MS: foundational and proximal. The foundational factors included resilience, cognitive and mental health, financial flexibility, and social support. Individuals with a greater number and/or amount of foundational factors were more likely to have proximal factors of healthy aging, which included work and social engagement, effective and accessible healthcare, healthy lifestyle habits, and maintaining independence at home. Social support was shown to be the most important foundational factor and mitigated the effects of not having other foundational factors. For example, those with more social support were able to remain independent at home longer even if they had fewer financial resources. Importantly, when friends and loved ones' homes, churches and other buildings were inaccessible by wheelchair, patients were more isolated. In addition, patients who were better off financially were able to work less or stop working earlier than others. Finally, individuals reported that, over time, their MS became less unpredictable because they became more familiar with their bodies and better understood their symptoms and how they changed.

Another survey study also supported the importance of social support. Using a longitudinal approach, Harrison and colleagues

surveyed 503 women aging with MS and found that within individuals, higher functional limitation was associated with lower social support (age range: 57 ± 10 years; 42% RR and 17% SP) [7]. Furthermore, between individuals, level of functional limitation was also associated with social support. Women with higher functional limitations and lower social support scores had more negative views of aging.

An earlier survey-based study by Gottlieb found that most older patients with MS felt they were aging successfully [16]. This investigator mostly attributed this to a positive outlook on life, gained wisdom, meaningful activity/relationships and ability to adapt in light of changing abilities (n = 45; ages 50–81 years). Some patients thought that MS predominated their experience so that the effects of aging were less noticeable, while others felt that aging complicated MS-related disability. Interestingly, many patients reported that older age made it easier to cope with their MS symptoms owing to reduced societal expectations of older individuals.

Other recent survey-based studies on aging patients with MS have asked patients about more specific topics. One such study asked MS patients of all ages about falls and found that 52% of patients had fallen in the last 6 months (n = 575; 52% RR and 22% SP) [17]. Patients more likely to have fallen had more neurological impairments and had moderate mobility restrictions, both of which are similar to those at greatest risk of falls in the general elderly population. In total, 62% of patients had concerns about falling, and 67% restricted their activity because of this. These high percentages and restriction in activity are also seen in the elderly. Overall, these survey studies are extremely informative in terms of the actual experiences of those aging with MS and what they have found to be positive and negative about their experiences.

Finlayson and colleagues asked patients (n = 279 dyads; ages 45–88 years) and their caregivers about their perceptions of their cognitive symptoms [18]. Approximately 61% of patients reported that cognitive symptoms interfered with their daily functioning. Those individuals who did report cognitive symptoms were more likely to be younger and also to report problems with depression. It is also possible that at least some of this higher reporting was due to a negative memory and/or reporting bias driven by depression in these individuals, as Bruce and Arnett have shown that depressed individuals with MS are characterized by a negative cognitive bias [19]. Almost 30% of dyads (patient and caregiver pairs) disagreed about the presence of cognitive symptoms. In half of these cases, patients did not believe they had cognitive deficits but the caregivers did. Interestingly, the longer the patient had been diagnosed with MS, the more likely there was to be a discrepancy, especially where the patient was not aware of cognitive difficulties and the caregiver was. One explanation given was that patients had grown more accustomed to their symptoms and were thus less aware of them. In addition, women were more likely to report a disagreement than men, especially where the patient perceived symptoms and the caregiver did not. Lastly, caregivers who spent more time with patients were more likely to report cognitive deficits. As the authors explain, these factors are important to consider since it can be very important that caregivers and patients are in agreement about symptoms in order to make the best decisions regarding care.

In sum, several recent studies suggest that many MS patients adjust well to aging and feel that through familiarity with their bodies and symptoms, a positive outlook, gained wisdom, meaningful relationships and activities, accessible healthcare, financial comfort, and healthy lifestyle habits, they can age successfully with MS. However, there are many salient problems patients report, including cognitive deficits, as well as falls and fear of falling that can restrict functioning.

Cognitive functioning

Cognitive deficits have been well documented in the general MS population. However, it is not yet clear if or how these difficulties change in prevalence or presentation as patients age. Smestad and colleagues used a cross-sectional design with patients who ranged from 45 to 81 years old (n = 28; mean age: 61 years; 29% RR and 59% SP), with an average of more than 30 years diagnosis duration [20]. Approximately a third were mildly disabled on the Expanded Disability Status Scale (EDSS; ≤3), and only 4% had moderate-to-severe depression (possibly a result of exclusion criteria).This study found that 48% of patients had cognitive impairment, defined as a score of 1.5 standard deviations below the mean on at least one subtest in two of the four main functional areas [20]. The typical pattern of cognitive deficits was moderate impairment on information processing speed, attention and

memory. Executive functioning was usually less affected. Interestingly, the cognitively impaired patients were younger at age of onset of their MS and thus had longer disease durations. This contrasted with previous studies showing no consistent association between cognitive functioning and disease duration [21–23]. This study also found course type to be a significant predictor of cognitive impairment, with SP patients performing worse than RR patients, a finding consistently reported by others [22].

Amato and colleagues reviewed longitudinal studies of cognitive functioning in MS and noted a dearth of well-controlled studies on this topic [22]. However, they describe that decline in cognition over time has been shown to be moderately related to progression of lesion load in the whole brain and in specific regions, as well as atrophy [24–27]. In one study, 21% of MS patients were found to have cognitive deterioration over a 3-year period [28]. However, in another study only 10% of patients declined cognitively over a 4-year period, although the most disabled patients were lost to follow-up (n = 33; age 48 ± 13 years) [29]. In an earlier study, Amato and colleagues found that cognitive deficits became more widespread over a 10-year period, with a higher percentage of patients showing impairments on multiple tests (n = 45; age: 39 ± 8 years at last testing; 58% RR and 31% SP) [30]. In their review, Amato and her colleagues conclude that cognition deteriorates fairly slowly in MS compared with other conditions, such as Alzheimer's disease, but the rates are variable and some patients also remain cognitively stable. In the long-term, progressive course and increasing disability were said to be associated with worse cognitive outcome.

A recent study focused specifically on processing speed and investigated its relationship with age in MS patients (n = 245; ages 18–74 years, mean: 45 years; 73% RR and 14% SP) [31]. Patients exhibited slower processing speed than controls on both the Color and Color–Word trials of a computerized Stroop task, as expected. These investigators divided patients and controls into five age cohorts and found that, cross-sectionally, patients were slower than controls and even the youngest age cohort of MS patients with the shortest disease duration was slower than the youngest controls. Furthermore, the youngest MS patients were significantly slower than the oldest controls. In addition, the rate of slowing in MS patients was parallel to that of controls. In other words, there was no significant age by group interaction; thus, MS and aging do not seem to interact to cause a more rapid decline than is seen in the general population. However, there were relatively few participants older than 60 years in this sample, so including more older participants might produce different results. In fact, there was a slight trend towards a larger group difference in the oldest cohort.

MS-related cognitive deficits can also complicate the diagnosis of cognitive disorders or dementia in the elderly. One study by Müller and colleagues (n = 40 MS patients; age: 61 ± 5 years, all SP) examined the differences in cognitive functioning between elderly patients with SP MS and otherwise healthy individuals with amnestic mild cognitive impairment (MCI) [32]. In amnestic MCI, impairments are limited to memory and do not significantly impact functioning. Müller and colleagues found that worse recognition memory in MCI patients was the only area that differentiated them from MS patients [32]. Areas that did not differ between participant groups were list learning, recall, intrusions, phonemic/semantic fluency, naming, praxis copy/recall, processing speed and cognitive flexibility, and overall mental status. Both groups performed worse on information processing speed and executive functioning than a healthy control group. In MS patients, but not patients with amnestic MCI, the authors found significant correlations between episodic verbal and visual memory recall, information processing speed and executive abilities. These investigators concluded that the retrieval problems seen in MS patients might be due to an executive/processing speed impairment, probably secondary to frontal GM atrophy, as opposed to the rapid forgetting seen in MCI, which is probably due to neuronal loss in the medial temporal lobes. One caveat the authors report is that MCI patients with high vascular burden had intact recognition. Clinically, this suggests that further evaluation is necessary if MS patients show poor recognition with poor recall. Further longitudinal studies are needed to better understand the specific cognitive changes seen over time and with progression of course type in MS. Imaging and histophathological studies can potentially help to characterize and understand these cognitive changes.

Psychological functioning/depression

While depression is known to be common in MS, few studies have examined depression in

aging MS patients, with mixed results. In the general population when compared with younger adults, older adults have generally been found to have lower rates of depression and anxiety [9], although this is difficult to disentangle owing to cohort effects and a general lack of longitudinal data. In a group of 739 MS patients, Chwastiak and colleagues (n = 739; age = 49 ± 11 years; 52% RR and 30% SP) found that relatively younger age was associated with clinically significant depression symptoms (Center for Epidemiologic Studies Depression Scale ≥16) [33]. Kneebone and Dunmore supported this and found that older adults with MS (n = 54 in both groups; age = 71 ± 5 years) reported significantly fewer depressive symptoms than younger adults with MS (age: 46 ± 8 years) [34]. These authors also measured cognitive style variables in these individuals and found that older patients had more MS-related helplessness (as measured by the MS Attitudes Index) than younger patients, but the groups did not differ on a measure of stress-related cognitions (Psychological Vulnerability Scale). Furthermore, the MS Attitudes Index and Psychological Vulnerability Scale both correlated positively with depression in older patients. The authors concluded that the decrease in depression in old age was not due to more adaptive cognitions or attitudes (in general or towards their MS), but that older patients might be less emotionally responsive.

On the other hand, some recent studies have found a positive association between age and depression in MS patients. Mattioli and colleagues found that depressed MS patients were older than those who were not depressed (n = 255; age: 40 ± 11 years; 88% RR and 12% chronic progressive) and da Silva and colleagues showed that age was positively associated with depression (n = 325; age: 16–70 years; 80% RR and 10% SP) [10,11]. Therefore, there are mixed results on the relative rates of depression in older MS patients and the inconsistent results are probably related to patient variables such as age range, course type and disability level.

Imaging & neuropathology

Although both MS patients and healthy aging adults have been shown to develop lesions and atrophy, there are also unique changes seen in each group. 'Incidental' ischemic WM lesions are common in the brains of the elderly [35]. They appear as hypodensities on CT and hyperintensities on T2-weighted and proton density MRI [36]. These lesions increase in frequency with age and have been shown to be negatively associated with cognitive performance [37,38]. Fernando and colleagues conducted a prospective post-mortem study of donated brains, examining them by MRI and pathology, to better understand the pathogenesis of these common lesions in the elderly. The authors concluded that such lesions probably resulted from a chronic hypoxic environment and were pathologically similar to the lesions seen in Alzheimer's disease [35].

Interestingly, one study found a normalization of inflammatory processes and neurodegeneration in elderly MS patients [39]. Specifically, Frischer and colleagues examined autopsies from a group of MS patients at different stages of the disease process (n = 67; age: 20–84 years, median: 76; 21% RR and 52% SP). They found a significant negative correlation between age or disease duration and inflammatory processes (density of T- and B-cell inflammatory infiltrates), and axonal injury. They also found that in older patients with longer disease duration, the density of T- and B-cell inflammatory infiltrates and extent of axonal injury (dystrophic axons in lesions) declined to levels similar to those found in age-matched controls. This occurred even in the context of significant disability (median EDSS: 8.5). In addition, when patients were separated into pathologically active or inactive based on classical active or slowly expanding lesions, those with inactive disease were significantly older and had significantly longer disease duration, while their disability at time of death was similar. The authors concluded that in older MS patients in the late stage of the disease, the inflammatory process may 'die out' and decrease to levels seen in age-matched controls and with it, neurodegeneration also declines to rates seen in controls. This assumes that there is no confounding age-related disease present, such as Alzheimer's disease or vascular disease. Indeed, the study did find that, among pathologically inactive patients, those with concomitant Alzheimer's disease pathology showed more acute cortical and WM axonal injury.

Besides lesions, atrophy is also a common phenomenon in both MS and aging. Overall, widespread GM loss is seen consistently in MS and age-related dementia and occurs early in the disease process [4]. However, brain volume loss occurs faster in MS patients than controls, at 0.5–1% per year [40,41] versus 0.1–0.3% per year in controls [42,43]). Regarding volume loss in more specific areas, thalamic volume has

been used as a marker for MS disease progression; however, volume changes due to aging can make interpretation of changes difficult in an MS sample with a broad age range [44]. Hasan and colleagues studied thalamic volume in a large group of MS patients (n = 109; age: 21–69 years; 81% RR and 11% SP) and controls [44]. Overall, they found that age correlated positively with EDSS and total brain lesion volume. They also found that normalized thalamic volume decreased with age in both groups. However, thalamic volume loss in MS patients correlated with disability even after adjusting for natural aging-related volume loss and whole-brain lesion volume. This suggests a contribution of the MS disease process to reduced thalamic volume that goes beyond aging. In general, it is likely that age and/or disease duration has an additional impact on atrophy and other changes in aging MS patients and also might affect the relationship between this neural damage and clinical presentation. For instance, one study concluded that gray matter atrophy was more related to cognitive deficits as MS progresses [45].

Besides structural changes, some studies have found similar functional changes in MS and aging. Hawallek and colleagues examined functional connectivity in MS patients and controls (n = 16; age: 23–46 years, 75% RR) , which is the temporal correlation between activity levels in separate brain regions [46]. They found that in MS patients, similar to what is seen in aging, there is increased functional connectivity between distinct neural systems. In other words, the authors explained that "cognitive representations such as receptive fields get gradually less specific and more broadly tuned." Furthermore, they found that this 'desegregation' correlated with cognitive deficits. Others have shown this dedifferentiation in connectivity in healthy aging and have attributed this partly to gray matter atrophy and demyelination, both of which are obviously present in MS [47]. Interestingly, the authors discuss how the neuropathology seen in aging and MS as both gradual and diffuse, as opposed to the often focal complete destruction of connectivity that is seen in other neural injuries and processes.

Conclusion & future perspective

This review outlines the positive and negative changes seen in individuals aging with MS. Both MS and aging are characterized by gradual, diffuse brain changes that often lead to a multitude of symptoms across many systems. Research on both MS and aging thus inform the other. And while similarities between these groups can act as exacerbating factors in those aging with MS, it seems that in some circumstances those with MS are more adept at coping with the changes seen with aging. However, there are key differences between these groups, including the early onset and sometimes unpredictable nature of MS, along with important neuropathological differences, and it is not clear exactly how these differences affect the psychological experiences of those aging with MS.

Future longitudinal work on aging MS patients will shed greater light on these important issues and better inform treatment. Recent advances in imaging technology, including functional connectivity, will be instrumental in understanding the neuropathological changes seen in these individuals. However, survey studies such as those described will remain crucial to understanding the patients' own experiences and those of their caregivers. A resiliency framework should be used alongside a deficits model, considering the many positive experiences and successful aging reported in so many studies of MS.

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