

Time as Passing in Multiple Sclerosis: In Need of Older Patients Multipl Sklerozda Zaman Geçiyor: Yaşlı Yetişkinlerin İhtiyaçları

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The phenomenon of aging is becoming increasingly significant on a global scale. It thus follows that the issue of health problems assumes greater significance. As organ functions decline, comorbidities, particularly chronic ones, become highly prevalent. Additionally, advanced age has numerous implications for the disease course, spanning from onset to therapeutic approaches through age-related immune changes and inflammaging, the burden of the disease on individuals and their caregivers, as well as challenges associated with geriatric syndromes and comorbidities. As such, a chronic disease that can lead to essential changes in an individual's life may become a critical health issue that requires holistic care for older adults (1). Furthermore, increasing life expectancy also causes a multitude of diseases to be more prevalent in adults.

Multiple sclerosis (MS), one of those diseases, is a chronic autoimmune neurodegenerative condition characterized by inflammation, demyelination, and axonal degeneration (2). The number of patients is estimated to be nearly 3 million worldwide (3). Classically, MS is more prevalent in young adults, of which the first symptom is revealed between the ages of 20 and 40. The first clinical demyelinating event may also occur after 50, referred to as late-onset MS, and after 60, referred to as very late-onset MS. However, it is

noteworthy that the onset of MS tends to shift towards older ages and is increasingly becoming prevalent in older adults, which is due to the fact the availability of numerous high-efficacy therapies (HETs) that may benefit the early stages of the disease, as well as symptomatic treatment options. Accordingly, despite a short interval to diagnosis, the prevalence of the patients with late-onset MS was 1% before 1991; however, it was reported to exceed nearly 10% after 2010 (4). In summary, both the prevalence of older adults with MS and late-onset MS cases is increasing considerably. Therefore, the influence of age-related physiological, immunological, and pathological changes on the disease should be considered in managing older adults with MS.

Among older individuals with MS, particularly those older than 65, approximately two-thirds of the patients are more likely to have a progressive course (either primary, secondary, or relapsing progressive) (5) characterized by progressive neurological disability, with only occasional plateaus or temporary minor improvements (6). Additionally, it is well known that older MS patients have a higher rate of disability progression (7). Recent evidence demonstrated that older age was associated with a greater probability of reaching irreversible Expanded Disability Status Scale (EDSS) scores of 4.0 or 6.0 and a faster rate

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of progression to irreversible disability for MS (8). [*EDSS score 4: significant disability but self-sufficient and up and about 12 hours a day. Able to walk without aid or rest for 500m; EDSS score 6: requires a walking aid - cane, crutch, etc. - to walk about 100m with or without resting* (9)].

Indeed, in the disease course, older age is associated with disability degree in itself, probably due to recurrent focal inflammation and diffuse chronic neurodegeneration based on accelerated age-related mechanisms. (10). The disease commonly initiates with motor and coordination problems similar to prevalent symptoms in older adults due to many comorbidities, such as musculoskeletal, neurodegenerative, sensorial, and vascular disorders, which may delay diagnosis. On the other hand, clearly, as well as age-related changes, prevalent comorbidities in older individuals also substantially may rapidly and gradually raise the degree of older MS patients' disability (11,12).

Older MS patients with multiple comorbidities require specialized care. This care is not only for avoiding new signs and symptoms always attributed to MS but also for improving the degree of disability and reducing disability accumulation in older MS patients. This approach may also help address and manage many accompanied geriatric syndromes, particularly polypharmacy, in these patients. More than one in four patients with MS met the criteria for polypharmacy, and hyper-polypharmacy affected 1 in 20 of the MS patients. Antidepressants, antiepileptics, and drugs for peptic ulcer/gastro-esophageal reflux disease were found to be most frequently contributed to polypharmacy (13). Polypharmacy, having multidimensional safety and clinical and economic implications, is associated with adverse health outcomes (14). Thus, optimizing drug therapy is one of the critical components of a holistic approach in older MS patients. In our clinical experience, the extent to which older MS patients need guidance to rationalize their pharmacotherapy is more than that of those with any other comorbidity. This underscores the crucial role of healthcare providers in providing specialized care for older MS patients.

The McDonald's criteria have been the guide for diagnosing MS since 2001, and the 2024 revisions to the

McDonald's criteria have been announced. These revisions include stricter criteria for older adults, which may make it more challenging for older patients to meet the diagnostic criteria. However, the revisions aim to diagnose the disease earlier and accurately, potentially leading to faster treatment. From the perspective of older patients with MS, the issue may be challenging considering that these patients will also get disease-modifying therapies (DMT), in particular, HETs earlier to prevent disability accrual on one side, and a known fact for HETs in older patients with MS that is to say a diminished efficacy of the drugs, less benefit with risk concerns when compared to their younger counterparts on the other side.

Within this context, older patients with MS have a higher prevalence of gray matter lesions and spinal cord lesions, faster brain volume loss during follow-up, and reduced neuron density pathologically. And the disease is more likely to be oriented toward neurodegenerative features (15). Although randomized controlled trials exclude MS patients over 55 years and relevant data derived from observational real-life studies, current DMTs are not sufficient enough to target neurodegeneration or disability progression. At that point, aging-driven mechanisms associated with the immune system, immunosenescence occurring prematurely in MS, age-associated low-grade chronic inflammation, and inflammation are crucial actors. Neuroinflammation mechanisms such as synaptopathy and synaptic plasticity impairments, which are the brain's ability to change and adapt, are also exacerbated and accelerate with age in MS patients (16,17).

A broader knowledge is needed regarding the impact of age on the immune system and disease progression. This understanding is crucial to provide effective therapeutic opportunities to effectively target the aging-driven mechanisms associated with the immune system, immunosenescence occurring prematurely in MS, age-associated low-grade chronic inflammation, and inflammaging, addressing the unique challenges of older patients with MS. Late-onset MS has its own unique traits, and there are specific considerations for older patients with MS. Healthcare providers should be aware of the

importance of the early detection and intervention for older adults, considering the physiological and immunological changes associated with aging that affect the disease manifestation and progression. It is evident that this approach may engender highly individualized treatment strategies for such patients. Furthermore, it should be kept in mind that a comprehensive approach is essential for managing MS in older populations, addressing not only the disease itself but also the associated comorbidities and geriatric syndromes that significantly impact patient outcomes. Such a holistic approach will be a salient factor for optimizing care and ensuring a better quality of life for older adults living with MS.

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