Review

Chronological Age and Biological Age: Relevance in Multiple Sclerosis

Patricia Mulero *, Alba Chavarría-Miranda, Nieves Tellez

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Chronological Age and Biological Age: Relevance in Multiple Sclerosis

Patricia Mulero, Alba Chavarría-Miranda and Nieves Téllez

Neurology Department, hospital Clínico Universitario de Valladolid, Spain.
* Correspondence: pmulero@saludcastillayleon.es

Abstract: Chronological age (C-Age), determined by the time elapsed since the birth of an individual, is considered as one of the main risk factors for the onset of multiple sclerosis (MS) and for its prognosis. On the other hand, biological age (B-age), conditioned by genetic, lifestyle, comorbidity, and environmental factors, defines the aging of tissues that contributes to the decline of organ function, the loss of functional reserve, and decrease in the regenerative capacity. In this context immunosenescence is increasing evidence as a factor that contributes to MS progressive course and loss of efficacy to MS drugs. B-Age can be estimated through different measurement strategies such as telomere-length, epigenetic-clocks and biomarker-composites. These biomarkers are gaining attention in MS since they seem to be associated with disability progression and are modulated by lifestyle changes.

Keywords: multiple sclerosis; biological age; chronological age; telomere length; epigenetic changes; senescence; aging; senolytics; lifestyle

Highlights

- Chronological age is a main factor for progressive phenotypes in multiple sclerosis (MS) patients, however there is a heterogeneity in prognosis that could be influenced by biological age.
- Leukocyte telomere length and epigenetic clocks are well-recognized somatic markers for biological aging and seem to be associated with disability progression in MS.
- Immunosenescence pathways could contribute to MS progressive course and loss of efficacy of disease treatments. Evidence with senomorphic and senolytic drugs is still scarce but is growing and it could be considering a potential therapy for MS in the future.
- Lifestyle changes could modulate biological age and hypothetically impact on MS course. Research must go further on this possibility.

1. Introduction

Chronological age (C-Age), determined by the time elapsed since the birth of an individual, is one of the main risk factors for the development of neurodegenerative diseases and for their prognosis [1]. However, there is still a great heterogeneity in the clinical outcomes despite the classical concept of age [2]. In this context, in the last years is gaining ground the concept of biological age (B-Age). B-Age is a less well-defined parameter that measures tissue damage, functional reserve capacity and regenerative potential [3]. This aspect is determined by genetic factors but also, modifiable by lifestyle habits, which translate that aging is a "plastic" phenomenon (Figure 1) [4]. According to B-Age, an individual can show an "accelerated" or "decelerated" aging in comparison to C-Age which influences and modulates the risk of developing a disease or the disease course [4].

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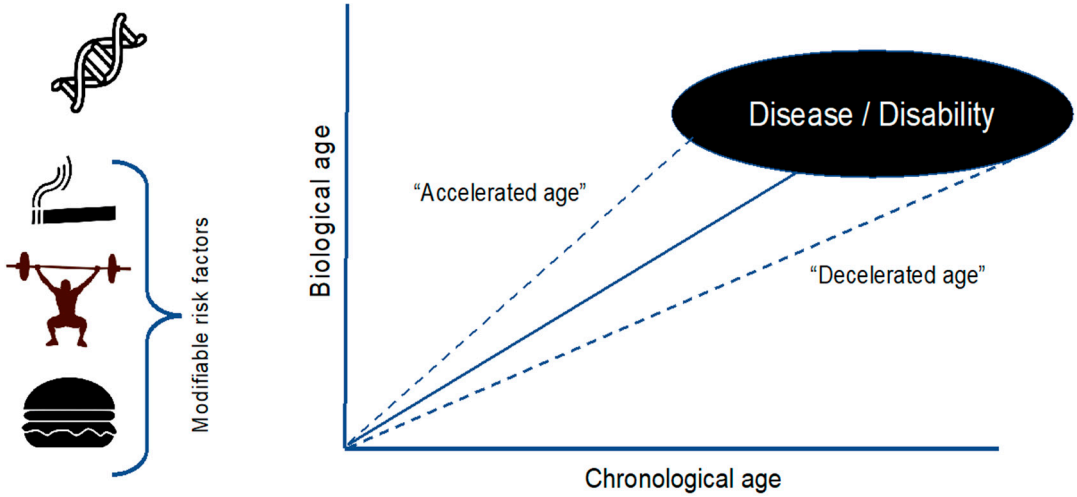

Figure 1. Relation between chronological age and biological age. Biological age is determined by genetic and modifiable factors that accelerated or decelerated aging.

Multiple sclerosis (MS) is a disease with a broad clinical phenotype, where some patients acquire an early disability and others remain progression free for the rest of their lives. There are well-known radiological and clinical prognostic factors that impact on the disease course, and C-Age seems to be also determinant. However, once again, individuals of the same age show a significant heterogeneity in the disease course despite sharing similar baseline prognostic factors. A hypothetical explanation to, at least part of this disparity, lies in the individual B-Age. This article reviews the significance of C-Age in MS and the growing relevance of B-Age in this neurodegenerative disease.

2. Impact of Chronological Age on Multiple Sclerosis

C-Age is a high impact factor on the incidence of MS. The highest incidence rate appears between 20 and 40 years of age, although the disease can onset at any age of lifespan [5]. Approximately, 2-5% of patients have a pediatric disease (under 17 years) [6] and an estimated 8-10% of patients debut over 50 years of age, which is called "late onset" [7]. These two populations of MS patients show a significantly different clinical phenotype. In between these two extremes, there is a continuum of intermediate course trajectories.

Meanwhile pediatric MS patients evolves almost exclusively with a relapsing course, older patients carry a higher risk of developing progressive disease phenotypes with a lower annualized relapsing rate [8–10]. Also, it is well known, that children with relapsing MS onset take longer to reach a progressive phase of disease in comparison to adults, however this occurs at a younger age [8]. That means that patients with a history of pediatric MS accumulate physical and cognitive disability at a younger age than patients with adult MS onset [11,12]. In addition, the average age at diagnosis of progressive MS in adults is 10 years older than that of relapsing forms, and age at onset of progression is highly similar between primary progressive and secondary progressive disease [13–15]. On the opposite, older patients experience shorter latency to progression and are more likely to experience incomplete disability recovery following relapses [16]. These observations suggest a strong relationship between C-Age and disability progression. On the other hand, it is well known that some MS patients remain free of disability progression until older ages, or even progression free. This suggest that C-Age is just a key player but not the only one and that there are other aspects influencing progressive phenotypes.

3. Biological Age in Multiple Sclerosis: What We Know

Aging is a natural process primarily caused by a progressive accumulation of deleterious changes to the normal metabolism at a molecular, cellular, and tissue levels, exacerbated by

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environmental toxics and unhealthy lifestyles. These damages finally act on the tissue functions and tissue capacity of regeneration. The "functionality" of tissues and organs is what we name B-Age. Defining a patient's biological age may offer more precision in determining the role of aging process than C-Age. Scientific evidence supports this statement in different diseases such as breast cancer [17] but also in stroke and neurodegenerative disease like dementia [18,19].

A recent meta-analysis of 13 cohorts found that epigenetic changes in DNA, one of the main process that drives B-Age, predicts all-cause of mortality, independent of C-Age and even after adjusting for traditional risk factors [20]. Another recent systematic review and meta-analysis have observed that epigenetic alterations were significantly related to mortality of cardiovascular disease, cancer and diabetes [21].

B-Age can be estimated through different measurement strategies. Biomarkers corresponding to metabolic activity or inflammation correlate with biological functions rather than C-Age and therefore might predict the functional capacity of a tissue or organ. Three main system measures have been proposed: telomere-length (TL), epigenetic-clocks and biomarker-composites. However, a single best measure of biological aging does not exist. Several authors have studied the correlation between these different techniques with not conclusive results [22]. A possible explanation to this disparity it that TL, the diverse proposed epigenetic clocks and biomarker-composites reflect different molecular hallmarks of aging and each of them may have its own strengths in the analysis of disease-specific mechanisms [23].

3.1. Telomere-Length

Telomeres are protein structures and nucleotide repeats (TTAGGG) localized at the edge of chromosomes. They shorten with each cell division and are necessary for the stability and protection of genomic DNA [24,25]. Telomeres are involved in signaling pathways that regulate cell proliferation, thus establishing the lifespan of a cell. Hence, they are considered biological clocks that determine the number of divisions that a cell undergoes [26]. In this process, it is essential the function of the telomerase enzyme, a ribonucleoprotein that helps in the maintenance of the telomere length. The activity of the telomerase enzyme is limited in most somatic cells, causing the telomeres to shorten, which finally leads to replicative senescence, an irreversible arrest of the cell cycle which is a main mechanism underlying aging. Evidence points out that besides C-Age, certain lifestyle factors such as smoking, obesity, inactivity, and unhealthy diet can increase the pace of telomere shortening [27] as well as chronic inflammation and oxidative damage which may compromise the cellular functions [28].

Several studies support the association between telomere length (TL) with cardiovascular diseases [29], dementia [30], and autoimmune diseases such as lupus or arthritis rheumatoid [31]. Relation between telomere length and MS have also been explored. A systematic review [32] analyzed 6 studies and found that four of them [33–36] reported significantly shorter leukocyte's telomere length, and observed differences compared to healthy controls (p=0.003 in meta-analysis). In this review, shorter telomeres in patients with MS were found to be associated, independently of age, with greater disability, lower brain volume, increased relapse rate and more rapid conversion from relapsing to progressive MS. This systematic review highlighted that people with MS typically have shorter telomeres in blood cells as compared to controls and it has been argued that the measurement of TL may serve as a potential biomarker for assessing and predicting clinical phenotypes of MS [32].

In recent years, various articles have been published attempting to link telomere length with the risk of developing multiple sclerosis through Mendelian randomization analysis. To date, the results are controversial, as two of the studies have shown an association between shorter telomere length and a higher risk of MS [37,38], while a third study describes longer telomere length as being associated with an increased risk [39]. It is necessary to delve deeper into the pathogenic mechanism of telomere length and its possible relationship with the risk of developing MS.

3.2. Epigenetic Clocks

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Another biomarker of B-Age is related to the critical role that epigenetic changes play in aging. There are a huge number of B-Age measurements systems called "epigenetic clocks" based on methylation patterns in different DNA regions [40]. This DNA methylation (DNAm) refers to heritable but modifiable mechanisms of genetic regulation that represent an interface for environmental and genetic factors to influence the genome. Multiple types of epigenetic clocks have been created to express B-age in healthy individuals and those living with chronic illness such as MS. The discrepancy between DNAm age and C- Age is determined by regressing the epigenetic age on C-age and is termed epigenetic age acceleration (EAA).

One of these epigenetic clocks called "PhenoAge" was compared with other 3 measures of epigenetic changes using blood samples from individuals diagnosed with MS [41]. This study showed that the different measures reflect separate pathophysiological aspects of the disease and that people with MS have significantly higher EAA than healthy controls when evaluating DNAm PhenoAge in whole blood, independently of body mass index or smoking. Other study [42] have observed that epigenetic age is accelerated in glial cells from brain tissue samples of MS participants compared with healthy controls.

The most recent epigenetic clock, the GrimAge clock, has been used to assess EAA in 583 MS patients in comparison to 643 non-MS controls. In this study The MS group exhibited an EAA increase of 5.1 years in cases with MS compared with controls [43].

These collective data suggest that according to epigenetic changes aging is accelerated in MS and may contribute to the pathology and disability severity.

3.3. Biomarker-Composites

In contrast to TL or epigenetic clocks, multi-biomarker approaches have been shown to be easily available measures of B-Age. They capture the global effects related to aging processes in multiple organ systems [44]. These multi-marker approaches have been successful in predicting mortality and estimating risk for aging related diseases, including cardiovascular disease [44].

The 10-item US National Health and Nutritional Survey (NHANES) multimarker index of biological age is a composite measure based on the analysis from every patient of specific biological and clinical data: creatinine, C-reactive protein, blood-urea nitrogen, albumin, alkaline phosphatase, cholesterol, CMV IgG, hemoglobin A1c, Forced Expiratory Volume in 1-sec (FEV1) and blood pressure. This multimarker index has been tested in 51 MS patients [45] finding that MS participants were biologically older than their age-matched controls.

4. MS Progression and Aging

Although clinical progression often manifests later in life and with longer disease MS duration, there is a growing body of evidence demonstrating that neurodegeneration and progression occurs from disease onset [46]. This means that neurodegenerative mechanisms are active much before the occurrence of the clinical progressive course and gradually become more evident by growing older (Figure 2). From a clinical point of view, and to date, the main aspects that clinicians take into account when evaluating the prognostic risk of a given patient are radiological parameters and some biological and demographic baseline data [47]. They are useful, but not enough to well classify patients and understand the heterogenic trajectories of progression. There should be additional aspects that influence the disease progression phenomenon, a fact that run in parallel with the fact of turning years.

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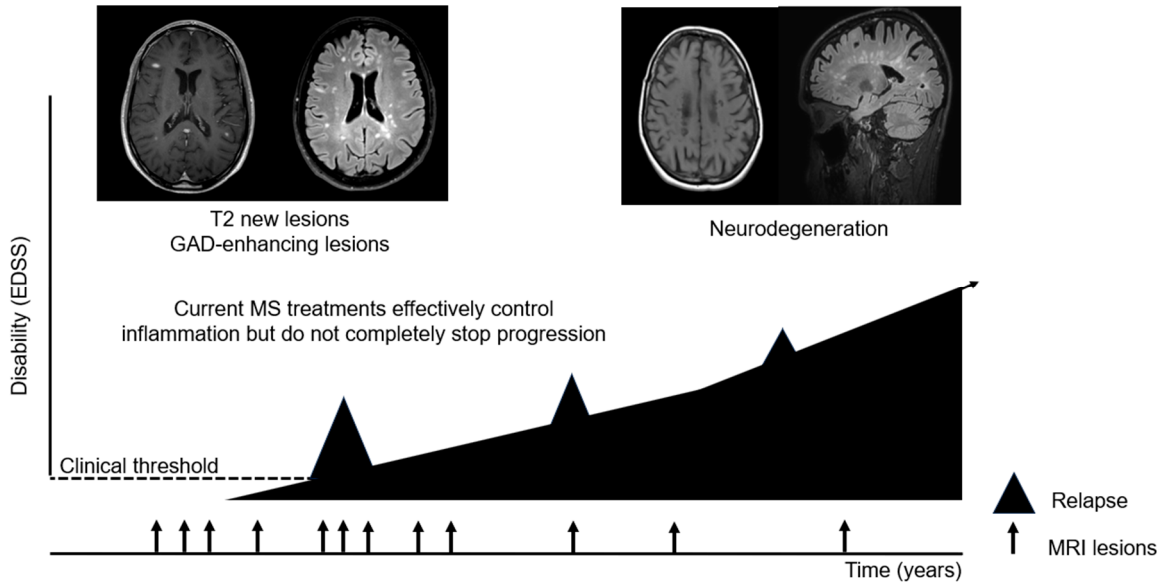

Figure 2. Multiple sclerosis disease evolution. Neurodegenerative and inflammatory mechanisms are both active since disease onset.

During the natural aging process, the immune system undergoes drastic changes in composition and functionality. This process, called immune senesce, results in reduced adaptive immune response, increased susceptibility to infections and increased non organ-specific autoantibody production [48]. Senescent cells are broadly characterized by cell cycle arrest and apoptotic resistance. Most cells undergoing senescence develop a senescence-associated secretory phenotype (SASP) characterized by the production of catabolic factors [49]. Independent of age, senescence can be induced in response to a variety of stimuli, including telomere attrition, oncogenes, and cell stress (e.g., oxidative, genotoxic, cytokines), which can contribute to SASP activation and senescence transformation [49]. These phenotypic changes culminate in systemic inflammation, loss of regenerative capacity, favoring an ultimately tissue degeneration. In MS patients senescence have a doble effect, in the periphery and in the central nervous system, resulting in reduced adaptive immune response, reduced capacity of remyelination and tissue reparation, reduced efficacy of disease modyfing treatments and increase the risk of treatment side effects such as infections [50,51].

5. Senomorphic and Senolityc Drugs in Multiple Sclerosis

Improving the understanding of relationship between aging and MS progression is important because targeting aging-related mechanisms could be a potential therapeutic strategy for MS.

Senotherapy is an emerging field of research for the development of possible treatments and strategies specifically targeting cellular senescence. There are currently more than 30 compounds that target senescence pathways [52]. One of them, the senomorphics, modulate cellular senescence through suppression of SASP without causing apoptosis. Senomorphics can be divided into several subtypes based on mechanism of action including mitochondrial antioxidants, Wnt/B-catenin inhibitors, JAK inhibitors, sirtuin regulators, mTOR inhibitors, or AMPK activators [53]. There are multiple studies in EAE, the experimental autoimmune encephalomyelitis mouse model of MS, that show that these compounds alleviated clinical disease and decreased demyelination [51–54]. In MS patients there are few early-phase clinical trials with senomorphics drugs, most of them with unreported data and just some in progressive forms without clear conclusions [54].

Another class of therapeutics commonly used to target senescence pathways are senolytics. Senolityc are drugs that selectively initiated apoptosis in senescent cells by inhibiting the pro-survival mechanisms upregulated during senescence. These upregulated pathways were discovered by bioinformatics and transcriptomics of senescent cells developing different generations of senolytic

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drugs [58]. Currently there are not senolityc clinical trials in MS. To the best of our knowledge, there are 2 ongoing recruiting phase II clinical trials in other neurodegenerative disease such an Alzheimer disease with the drug combination of dasatinib and quercetin [59]. In EAE, there is just one report [60] with a senolytic called BCL2 inhibitor, Navitoclax, that significantly reduced the presence of senescent microglia in the EAE model. This treatment had an effect on EAE mice, decreasing motor symptoms severity, improving visual acuity, promoting neuronal survival, and decreasing white matter inflammation.

Disease-modifying treatments currently in use for MS are immunomodulatory and immunosuppressive medications aiming to protect the CNS from immune-mediated damage. There is an urgent unmet need for neuroprotective strategies. Emerging in vitro and preclinical data in other disease suggest that targeting cellular senescence may promote repair, remyelination and neuroprotection and this also could work for MS and other demyelinating disease. However, evidence of its effectiveness is still in its infancy, as is evidence of its potential toxicity. For example, dasatinib, is a senolytic EMA approved drug [61] for treatment of chronic myeloid leukemia and lymphoblastic leukemia, which has been related to the development of adverse effects such as cytopenias or pleural effusion. The toxicity of this drugs in MS needs to be stablished.

6. Lifestyle Habits and Biological Age

As we have previously described, B-Age is influenced by genetic factors and, what is more valuable, by modifiable factors such as lifestyle (Figure 1).

Among these factors, there is scientific evidence on how physical exercise, smoking or obesity impact biological age markers in healthy people.

Studies of the relationship between telomeres and exercise have described a high telomerase activity and a reduced rate of telomere attrition in endurance athletes, compared to inactive controls [62]. Also, it is reported that telomere length shortening can be reduced with moderate levels of physical activity, compared to inactivity in healthy people [60]. A recent systematic review and meta-analysis suggested that the type of exercise is relevant and found that a high-intensity interval training have a higher positive effect on telomere length compared with other types of exercise such as resistance training or aerobic exercise in a healthy population [64]. The positive effect of exercise have also been observed on other B-Age markers as epigenetic clocks [65].

Smoking increases oxidative DNA damage and thus influences telomere shortening. A meta-analysis including 30 studies confirmed significantly shorter TL in peripheral blood cells among ever smokers compared to never smokers and among current smokers compared to former smokers in people without other pathology [66].

Obesity in childhood and adolescence is a significant risk factor for MS and is partly a consequence of unhealthy eating behavior and sedentary lifestyle. A recent systematic review of 16 articles [67] found a negative association between childhood obesity and TL.

However, the interplay of physical activity, smoking or obesity and B-Age among patients with MS has not been elucidated. Additional prospective research is needed to clearly define how lifestyle changes can slow down disease progression.

7. Conclusion and Final Remarks: Unveiling the Future Directions

The influence of age and aging on the MS course has been highlighted since the early epidemiological studies. Notably in the last years a growing evidence suggest that the speed and way of aging could modulate the speed of MS progression and the relevance of biological age is growing in MS and other age-related diseases.

The measurement of biological age, however, faces several problems. Firstly, the techniques used are not easily accessible and there is a low agreement between their results. Secondly, the use of drugs whose objective is to reverse senescence is very far from showing significant efficacy in patients with MS and other neurodegenerative diseases.

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The speed of aging can be influenced, at least in part, by our lifestyle, a modifiable issue. On the other hand, current approved therapies for MS do not stop progression, and the elderly MS population is increased in our centers. We need to generate evidence about the impact that a healthy lifestyle, an affordable "add-on therapy" for all patients, has on biological age, aging and hypothetically on disability progression in MS patients.

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