

## AGING AS A MODULATOR OF MULTIPLE SCLEROSIS PATHOPHYSIOLOGY

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## SAŽETAK

Populacija starijih pacijenata sa multiplom sklerozom se značajno povećava, uključujući osobe sa kasnim (nakon 50. godine) i veoma kasnim (nakon 60. godine) početkom bolesti. Starenje moduliše imunski i nervni sistem, doprinoseći transformaciji kliničkog toka u progresivni obrazac i povećanju rizika za razvoj progresije bolesti nezavisno od relapsa (PIRA). Takođe, multipla skleroza sa početkom u kasnijem životnom dobu karakteriše se češćim progresivnim fenotipom, manjom pojavom inflamatornih relapsa i kraćim vremenom do ostvarivanja invaliditeta. Starenje imunskog sistema (imunosenescencija) dovodi do sužavanja raznovrsnosti T-ćelijskog receptorskog repertoara, promena u broju i funkciji CD4+ i CD8+ T-limfocita, kao i do disbalansa u odnosu efektorskih i regulatornih T-limfocita. Na nivou centralnog nervnog sistema starenje doprinosi neurodegeneraciji kroz povećanu degeneraciju oligodendrocita, disfunkciju mikroglije, akumulaciju gvožđa, oksidativni stres, disfunkciju mitohondrija i smanjenje neuroprotektivnih mehanizama. Smanjena proliferacija i diferencijacija neuralnih stem ćelija, kao i strukturne i funkcionalne promene glutamatnih receptora, prevashodno N-metil-D-aspartat receptora, dodatno kompromituju neuroprotektivne i reparativne mehanizme. Razumevanje interakcija starenja i patofizioloških mehanizama multiple skleroze ključno je za razvoj ciljanih terapijskih strategija za sve brojniju populaciju starijih pacijenata sa multiplom sklerozom. Cilj ovog rada je da, kroz integrativni pregled dostupne literature, sagleda ulogu procesa starenja u modulaciji ključnih patofizioloških mehanizama multiple skleroze.

**Ključne reči:** starenje, multipla skleroza, imunosenescencija, neurodegeneracija

## ABSTRACT

The number of older patients with multiple sclerosis is rising significantly, including individuals with late-onset disease (after age 50) and very late-onset disease (after age 60). Aging affects the immune and nervous systems, contributing to a shift in the clinical course towards a progressive pattern and increasing the risk of disease progression independent of relapse activity (PIRA). Additionally, late-onset multiple sclerosis is characterised by a more frequent progressive phenotype, fewer inflammatory relapses, and a shorter time to disability accumulation. Immune system aging (immunosenescence) leads to a reduced diversity of the T-cell receptor repertoire, changes in the number and function of CD4+ and CD8+ T lymphocytes, and an imbalance between effector and regulatory T cells. At the central nervous system level, aging contributes to neurodegeneration through increased oligodendrocyte degeneration, microglial dysfunction, iron accumulation, oxidative stress, mitochondrial dysfunction, and diminished neuroprotective mechanisms. Reduced proliferation and differentiation of neural stem cells, as well as structural and functional changes in glutamate receptors, primarily N-methyl-D-aspartate receptors, further compromise neuroprotective and reparative processes. Understanding the interactions between aging and the pathophysiological mechanisms of multiple sclerosis is crucial for developing targeted therapeutic strategies for the increasing population of older patients with multiple sclerosis. This paper aims to examine, through an integrative review of the available literature, the role of the aging process in modulating key pathophysiological mechanisms of multiple sclerosis.

**Keywords:** aging, multiple sclerosis, immunosenescence, neurodegeneration

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**Primljeno • Received:** January 29, 2026;

**Revidirano • Revised:** March 2, 2026;

**Prihvaćeno • Accepted:** March 10, 2026;

**Online first:** March 25, 2026

DOI: 10.5937/smcl7-64495

## UVOD

Prema podacima Internacionalne federacije za multiplu sklerozu od 2,8 miliona ljudi koji boluju od multiple skleroze, 1 od 10 osoba ima 65 godina i više. Multipla skleroza je bolest koja može trajati decenijama i većina ovih starijih bolesnika ima multiplu sklerozu duže od 20 godina [1]. Početak multiple skleroze je najčešće između 20. i 40. godine života, a relapsno-remitentni oblik bolesti pogađa oko 85% bolesnika [2]. Primarno-progresivna i sekundarno progresivna multipla skleroza počinju u sličnim godinama života tj. oko 45. godine i karakterišu se razvojem koji dovodi do akumulacije invaliditeta u sličnom vremenskom periodu [3,4]. Pokazano je da početni oblik bolesti, bilo da je reč o relapsno-remitentnom ili primarno-progresivnom obliku, zapravo ne utiče značajno na uzrast u kome dolazi do ostvarivanja ključnih faza invaliditeta [4]. Poslednjih decenija incidencija kasnog početka multiple skleroze tj. početka bolesti nakon 50. godine života se značajno povećala [5]. Takođe, uočeno je i značajno povećanje incidencije veoma kasnog početka multiple skleroze tj. nakon 60. godine života [6,7]. Kod pacijenata sa kasnim početkom multiple skleroze češće se javljao progresivni tok bolesti od samog početka [5].

Hronološko starenje predstavlja fiziološki proces, koji ima svoje reperkusije kako na centralni nervni sistem (CNS), tako i na imunski sistem. S druge strane, hronični inflamatorni proces i neurodegeneracija, koji su povezani sa multiplom sklerozom doprinose ubrzanom procesu biološkog starenja CNS [8]. Starenje imunskog sistema (imunosenescencija) pogađa kako urođeni tako i adaptivni imunski sistem. Posledice su brojne počevši od smanjenog imunološkog nadzora nad ćelijama koje su oštećene ili stare, preko promena u zastupljenosti i funkciji ćelija urođene imunosti, pa do izrazitih promena u T-ćelijskom kompartmanu [9,10].

Poslednjih godina uveden je koncept „progresije nezavisno od relapsne aktivnosti“ (engl. *progression independent of relapse activity*, PIRA), koji se odnosi na akumulaciju invaliditeta, bez prethodnog akutnog pogoršanja bolesti i koji ukazuje na neurodegeneraciju koja postoji nezavisno od zapaljenskog procesa u multiploj sklerozu [11]. U studiji Tur et al. (2022.) pokazano je da je stariji uzrast prilikom prvog napada bio u korelaciji sa većim rizikom od razvoja PIRA. Preciznije, rizik od razvoja PIRA se povećavao za 43% za svaku deceniju starosti više prilikom prvog napada [11]. Proces starenja povećava vulnerabilnost neurona, doprinosi akumulaciji oštećenja nervnog tkiva i istovremeno smanjuje njegovu funkcionalnu rezilijentnost i reparativni potencijal [12].

Cilj ovog rada je da, kroz integrativni pregled dostupne literature, sagleda ulogu procesa starenja u

## INTRODUCTION

According to the Multiple Sclerosis International Federation, of the 2.8 million of people living with multiple sclerosis worldwide, one in ten people are aged 65 years or older. Because multiple sclerosis is a chronic condition that can persist for decades, most of these older patients have lived with the disease for more than 20 years [1]. The onset of multiple sclerosis most commonly occurs between the ages of 20 and 40, and the relapsing-remitting form of the disease affects approximately 85% of patients [2]. Primary-progressive and secondary-progressive multiple sclerosis typically begin at similar ages, around 45 years, and are characterized by disease progression that leads to the accumulation of disability over a comparable period of time [3,4]. Studies have shown that the initial form of multiple sclerosis, whether relapsing-remitting or primary-progressive, does not significantly influence the age at which key stages of disability are reached [4]. In recent decades, the incidence of late-onset multiple sclerosis, defined as disease onset after the age of 50, has increased significantly [5]. A notable rise has also been observed in the incidence of very late-onset multiple sclerosis, with disease onset occurring after the age of 60 [6,7]. In patients with late-onset multiple sclerosis, the disease more frequently follows a progressive course from the very onset [5].

Chronological aging is a physiological process that affects both the central nervous system (CNS) and the immune system. Conversely, chronic inflammatory processes and neurodegeneration associated with multiple sclerosis contribute to an accelerated process of biological aging of the CNS [8]. Aging of the immune system (immunosenescence) affects both the innate and adaptive immune systems. Its consequences are numerous, ranging from reduced immune surveillance of damaged or senescent cells, through changes in the distribution and function of innate immune cells, to pronounced alterations in the T-cell compartment [9,10].

In the recent years, the concept of "progression independent of relapse activity" (PIRA) has been introduced. It refers to the accumulation of disability in the absence of a preceding acute relapse and indicates neurodegeneration occurring independently of the inflammatory process in multiple sclerosis [11]. The study by Tur et al. (2022) showed that older age at the time of the first attack was associated with a higher risk of developing PIRA. More specifically, the risk of PIRA increased by 43% for each additional decade of age at the first attack in patients with multiple sclerosis [11]. The aging process increases neuronal vulnerability, promotes the accumulation of neural tissue damage,

modulaciji ključnih patofizioloških mehanizama multiple skleroze.

## UTICAJ STARENJA NA REMODELOVANJE IMUNSKOG SISTEMA

Imunosenescencija predstavlja starenjem uslovljene strukturne i funkcionalne promene imunskog sistema, koje dovode do poremećaja njegove efikasnosti [13]. Starenje dovodi do promena u broju i funkciji imunskih ćelija, oslabljenog adaptivnog imunskog odgovora, održavanja niskostepene inflamacije i metaboličkih promena u imunskom sistemu [9,13].

Starenjem uslovljena involucija timusa, dovodi do progresivnog sužavanja perifernog repertoara naivnih T-limfocita. Ovaj deficit se delimično kompenzuje pojačanom homeostatskom proliferacijom i klonalnom ekspanzijom postojećih T-ćelijskih populacija, što rezultuje relativnom ekspanzijom memorijskog T-ćelijskog pula. Takvo remodelovanje adaptivnog imunskog sistema ima za posledicu smanjenu imunološku plastičnost i narušenu sposobnost generisanja efikasnih odgovora na nove ili tumorske antigene [14]. Homeostatska proliferacija i antigen-zavisna klonalna ekspanzija postojećih T-ćelijskih populacija predstavljaju mehanizme koji mogu omogućiti preživljavanje i ekspanziju autoreaktivnih T-ćelijskih klonova. Starenjem uslovljeno sužavanje raznovrsnosti T-ćelijskog receptorskog repertoara dovodi do narušene efikasnosti imunskog sistema i oslabljenih reparativnih mehanizama, čime se stvara okruženje pogodno za egzacerbaciju patološkog procesa i progresiju bolesti [15]. Pokazano je da starenje dovodi do značajnih promena u broju i funkciji CD4<sup>+</sup> i CD8<sup>+</sup> T-limfocita, pri čemu su ove promene izraženije u populaciji CD8<sup>+</sup> T-ćelija, kako kod ljudi tako i u animalnim modelima [16,17]. Takođe, starenjem dolazi do povećanja broja regulatornih T-ćelija kod ljudi [18], a sličan trend zabeležen je i u animalnim modelima multiple skleroze [19,20]. Funkcionalna aktivnost regulatornih T-ćelija ostaje nepromenjena ili je čak povećana starenjem kod ljudi [18]. Međutim, rezultati studija na životinjama sugerišu da je moguće da akumulacija perifernih regulatornih T-ćelija (CD4<sup>+</sup>FoxP3<sup>+</sup>) odlaže početak bolesti kod starih jedinki, dok nakon njenog nastanka smanjena migracija ovih ćelija u CNS onemogućuje adekvatnu kontrolu progresivnog toka bolesti [20]. Kod starih miševa sa indukovanim animalnim modelom multiple skleroze uočena je izraženija plastičnost regulatornih T-limfocita (CD4<sup>+</sup>FoxP3<sup>+</sup>), koja se ogleda u ko-ekspresiji interferona (IFN)- $\gamma$  i /ili interleukina (IL)-17 sa FoxP3, u poređenju sa mladim jedinkama [20]. Ovakva plastičnost regulatornih T-limfocita kod starih jedinki može dovesti do smanjenja njihove supresivne funkcije i posledičnog pojačavanja patoloških procesa u CNS-u.

and simultaneously reduces both functional resilience and the capacity for repair [12].

The aim of this paper is to examine, through an integrative review of the available literature, the role of the aging process in modulating the key pathophysiological mechanisms of multiple sclerosis.

## INFLUENCE OF AGING ON IMMUNE SYSTEM REMODELING

Immunosenescence refers to the age-related structural and functional changes in the immune system that result in impaired immune efficiency [13]. Aging results in alterations in both the number and function of immune cells, a weakened adaptive immune response, persistent low-grade inflammation, and metabolic changes within the immune system [9,13].

Age-related involution of the thymus causes a gradual reduction in the peripheral repertoire of naïve T lymphocytes. This deficit is partially compensated by increased homeostatic proliferation and clonal expansion of existing T-cell populations, leading to a relative enlargement of the memory T-cell pool. This remodeling of the adaptive immune system leads to diminished immune plasticity and a reduced capacity to mount effective responses against new or tumor antigens [14]. Homeostatic proliferation and antigen-driven clonal expansion of existing T-cell populations are mechanisms that can support the survival and expansion of autoreactive T-cell clones. Aging-induced reduction in the diversity of the T-cell receptor repertoire impairs immune system efficiency and weakens reparative mechanisms, thereby creating conditions that favor exacerbation of the pathological process and disease progression [15]. Studies have shown that aging causes significant changes in the number and function of CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes, with these changes being more pronounced in the CD8<sup>+</sup> T-cell population, both in humans and in animal models [16,17]. Aging also results in an increased number of regulatory T-cells in humans [18], with a similar trend observed in animal models of multiple sclerosis [19,20]. The functional activity of regulatory T-cells remains unchanged, or may even increase, with aging in humans [18]. However, findings from animal studies suggest that the accumulation of peripheral regulatory T-cells (CD4<sup>+</sup>FoxP3<sup>+</sup>) may delay disease onset in older individuals, while after onset, their reduced migration into the CNS limits effective control of the progressive course of the disease [20]. In aged mice with an induced animal model of multiple sclerosis, regulatory T lymphocytes (CD4<sup>+</sup>FoxP3<sup>+</sup>) exhibited greater plasticity, reflected by the co-expression of interferon (IFN)- $\gamma$  and/or interleukin (IL)-17 with FoxP3, compared to younger mice [20]. This plasticity

Pored toga, izražen disbalans između efektorskih i regulatornih T-ćelija može imati značajan uticaj na klinički tok multiple skleroze kod starijih bolesnika [18,20]. Ključni aspekti fiziološkog starenja T-limfocita prisutni su i kod pacijenata sa multiplom sklerozom [21,22]. Međutim, u studiji sprovedenoj na pacijentima sa multiplom sklerozom koji nisu prethodno dobijali imunomodulatornu terapiju, uočeno je značajno povećanje zastupljenosti aktiviranih i citotoksičnih CD4<sup>+</sup> T-limfocita, posebno kod pacijenata starijih od 60 godina [21]. Akumulacija citotoksičnih CD4<sup>+</sup> T-limfocita u starijoj populaciji bolesnika sa multiplom sklerozom može predstavljati važan patofiziološki mehanizam, imajući u vidu njihovu sposobnost da direktno oštećuju ćelije CNS-a i doprinose neurodegenerativnim procesima.

Sekretorni fenotip povezan sa senescencijom (engl. *senescence-associated secretory phenotype*, SASP) obuhvata skup funkcionalnih promena senescentnih ćelija, koje se manifestuju razvojem proinflamatornog fenotipa i povećanim oslobađanjem citokina, hemokina i drugih medijatora inflamacije [23]. U demijelinizovanim lezijama utvrđeno je povećanje ćelijske senescencije u mikroglijalnim ćelijama, koje je koreliralo sa smanjenim kapacitetom remijelinizacije kod starih miševa. Analiza SASP pokazala je povišenu koncentraciju hemokina C-C motiv ligand 11 (CCL11), poznatog i kao eotaksin-1 u lezijama starih jedinki, što je dovedeno u vezu sa narušenom maturacijom oligodendrocita [24]. Ovi nalazi sugerisu da bi ciljanje SASP faktora, poput eotaksina-1, naročito kod starijih bolesnika, moglo predstavljati potencijalni terapijski pristup za poboljšanje remijelinizacije u multiploj sklerozi.

## ULOGA STARENJA U NEURODEGENERATIVNIM PROCESIMA MULTIPLE SKLEROZE

Starenje je glavni faktor rizika za većinu neurodegenerativnih bolesti i predstavlja jedan od ključnih bioloških procesa koji modulišu neurodegenerativne mehanizme u multiploj sklerozi. Mehanizmi kojima starenje potencijalno doprinosi neurodegeneraciji uključuju genomsku nestabilnost, skraćenje telomera, epigenetske promene, poremećenu homeostazu proteina, disfunkciju mitohondrija, ćelijsku senescenciju, poremećenu regulaciju nutrijentne signalizacije, iscrpljenost matičnih ćelija i izmenjenu intercelularnu komunikaciju [25,26]. Hronični inflamatorni proces u multiploj sklerozi, u kombinaciji sa kompromitovanom remijelinizacijom, doprinosi aksonalnoj degeneraciji, progresivnoj atrofiji CNS-a i egzacerbaciji kliničke manifestacije bolesti [27].

Multipla skleroza sa kasnim početkom karakteriše se češćim progresivnim fenotipom, manjom pojavom inflamatornih relapsa i kraćim vremenom do ostvarivanja

of regulatory T lymphocytes in older individuals can reduce their suppressive function, leading to an increase in pathological processes within the CNS. Moreover, a marked imbalance between effector and regulatory T-cells may significantly influence the clinical course of multiple sclerosis in elderly patients [18,20]. Key features of physiological T-lymphocyte aging are also observed in patients with multiple sclerosis [21,22]. However, in a study of multiple sclerosis patients who were naïve to immunomodulatory therapy, a significant increase in activated and cytotoxic CD4<sup>+</sup> T lymphocytes was observed, particularly in patients over 60 years of age [21]. The accumulation of cytotoxic CD4<sup>+</sup> T lymphocytes in the elderly population of multiple sclerosis patients may represent a key pathophysiological mechanism, given their capacity to directly damage CNS cells and contribute to neurodegenerative processes.

The senescence-associated secretory phenotype (SASP) encompasses a set of functional changes in senescent cells, characterized by the development of a pro-inflammatory profile and increased secretion of cytokines, chemokines, and other inflammatory mediators [23]. In demyelinated lesions, increased cellular senescence was observed in microglial cells, correlating with reduced remyelination capacity in aged mice. Analysis of SASP revealed elevated levels of the chemokine C-C motif ligand 11 (CCL11), also known as eotaxin-1, in the lesions of older individuals, which was associated with impaired oligodendrocyte maturation [24]. These findings suggest that targeting SASP factors, such as eotaxin-1, particularly in elderly patients, may represent a potential therapeutic strategy to enhance remyelination in Multiple Sclerosis.

## THE ROLE OF AGING IN THE NEURODEGENERATIVE PROCESSES OF MULTIPLE SCLEROSIS

Aging is a major risk factor for most neurodegenerative diseases and one of the key biological processes that modulate neurodegenerative mechanisms in multiple sclerosis. Mechanisms through which aging may contribute to neurodegeneration include genomic instability, telomere shortening, epigenetic alterations, impaired protein homeostasis, mitochondrial dysfunction, cellular senescence, dysregulated nutrient signaling, stem cell exhaustion, and altered intercellular communication [25,26]. The chronic inflammatory process in multiple sclerosis, combined with impaired remyelination, contributes to axonal degeneration, progressive CNS atrophy, and worsening of the disease's clinical manifestations [27].

Late-onset multiple sclerosis is characterized by a more frequent progressive phenotype, fewer inflam-

invaliditeta [8,28]. Kod pacijenata kod kojih bolest započinje u mlađem životnom dobu, pokazano je da sa starenjem dolazi do smanjenja inflamatorne aktivnosti u CNS-u, nezavisno od dužine trajanja bolesti, što se klinički manifestuje redukcijom učestalosti relapsa [29]. Nasuprot tome, demijelinizacija i neurodegenerativni procesi postaju izraženiji sa starenjem bolesnika [8,30].

Veća životna dob u trenutku prvog kliničkog ispoljavanja multiple skleroze povezuje se sa povećanom verovatnoćom razvoja PIRA, što ukazuje na značajnu ulogu starenja u oblikovanju toka bolesti [31]. Savremena istraživanja pokazuju da se progresija bolesti može detektovati već u najranijim fazama multiple skleroze, pri čemu inflamatorni i neurodegenerativni mehanizmi funkcionišu kao deo jedinstvenog patofiziološkog kontinuuma u okviru kojeg se i pogoršanje vezano za relaps (engl. *relapse-associated worsening*, RAW) i PIRA javljaju od samog početka bolesti, dok starenje predstavlja jedan od ključnih modulatora kliničkog fenotipa bolesti [11,31].

Istraživanja na starim pacovima pokazuju da tokom starenja CNS-a dolazi do povećane degeneracije oligodendrocita i njihovih prekursora, što rezultuje gubitkom mijelina i sekundarno doprinosi razvoju aksonalne degeneracije [32]. Jedna od najizraženijih promena u oligodendrocitima povezanim sa starenjem jeste akumulacija oštećenja DNK, kojoj u značajnoj meri doprinose njihovi visoki metabolički zahtevi [33]. Ovi procesi dovode do smanjene sposobnosti remijelinizacije, čime se u multiploj sklerozi, naročito kod starijih bolesnika, dodatno pospešuje progresija neurodegenerativnih promena i akumulacija invaliditeta.

## UTICAJ STARENJA NA AKTIVACIONI STATUS I FUNKCIONALNU DINAMIKU MIKROGLIJE U MULTIPLOJ SKLEROZI

Starenje moduliše aktivaciju i zastupljenost mikroglije, posebno u području oko plaka kod pacijenata sa multiplom sklerozom [34]. Proces starenja utiče kako na strukturne, tako i na funkcionalne karakteristike mikroglije. Studije na životinjskim modelima ukazuju da mikroglijalne ćelije sa starenjem zadobijaju hronično aktivirani fenotip, praćen smanjenjem njihove fagocitne sposobnosti [35,36]. Pored toga, starenje kompromituje i njihovu ulogu u imunološkom nadzoru mikrookruženja, dovodeći do smanjene dinamičnosti i gubitka razgranatog morfološkog fenotipa [37]. Ove starenjem uslovljene morfološke i funkcionalne promene mikroglije, koje obuhvataju perzistentnu niskostpenu aktivaciju uz istovremenu fagocitnu disfunkciju, mogu predstavljati jedan od ključnih mehanizama koji su u osnovi PIRA, doprinoseći degeneraciji aksona u odsustvu izraženog akutnog inflamatornog procesa.

matory relapses, and a shorter time to disability [8,28]. In patients whose disease begins at a younger age, aging has been shown to be associated with a decrease in inflammatory activity in the CNS, regardless of disease duration, which is clinically manifested by a reduced frequency of relapses [29]. In contrast, demyelination and neurodegenerative processes become more pronounced with advancing age [8,30].

Older age at the time of the first clinical manifestation of multiple sclerosis is associated with an increased likelihood of developing PIRA, indicating a significant role of aging in shaping the course of the disease [31]. Recent research shows that disease progression can be detected even in the earliest stages of multiple sclerosis, with inflammatory and neurodegenerative mechanisms operating as part of a single pathophysiological continuum in which both relapse-associated worsening (RAW) and PIRA occur from the very beginning of the disease, while aging represents one of the key modulators of the clinical phenotype [11,31].

Research in aged rats shows that during CNS aging there is increased degeneration of oligodendrocytes and their precursors, resulting in myelin loss and secondarily contributing to the development of axonal degeneration [32]. One of the most pronounced age-related changes in oligodendrocytes is the accumulation of DNA damage, which is largely driven by their high metabolic demands [33]. These processes reduce the capacity for remyelination, which in multiple sclerosis, particularly in older patients, further accelerates neurodegenerative progression and disability accumulation.

## THE INFLUENCE OF AGING ON MICROGLIAL ACTIVATION AND FUNCTIONAL DYNAMICS IN MULTIPLE SCLEROSIS

Aging modulates microglial activation and abundance, particularly in the peri-plaque regions of patients with multiple sclerosis [34]. It affects both the structural and functional characteristics of microglia. Studies in animal models indicate that with aging, microglia acquire a chronically activated phenotype, accompanied by reduced phagocytic capacity [35,36]. In addition, aging impairs their role in immune surveillance of the microenvironment, resulting in reduced dynamism and a loss of their branched morphological phenotype [37]. These age-related morphological and functional changes in microglia, including persistent low-level activation with concomitant phagocytic dysfunction, may represent a key mechanism underlying PIRA, contributing to axonal degeneration even in the absence of pronounced acute inflammation.

Fiziološko starenje dovodi do akumulacije gvožđa u mikroglijalnim ćelijama. Takođe, kod pacijenata sa multiplom sklerozom, demijelinizacija oslobađa gvožđe iz oštećenih oligodendrocita i mijelina, koje potom preuzimaju mikroglijalne ćelije i makrofage. Posledično, dolazi do akumuliranja gvožđa u mikroglijalnim ćelijama, posebno na ivicama hronično aktivnih lezija. Ovo taloženje gvožđa povezuje se sa proinflamatornim fenotipom mikroglije, kao i povećanom sintezom slobodnih radikala kiseonika, što doprinosi hroničnoj neuroinflamaciji i progresivnoj neurodegeneraciji kod starijih bolesnika sa multiplom sklerozom [38].

## STARENJEM USLOVLJENE PROMENE REPARATIVNIH MEHANIZAMA U MULTIPLOJ SKLEROZI

Patofiziološki mehanizmi koji su u osnovi PIRA povezuju se sa kompartmentalizacijom inflamatornog procesa unutar CNS-a, uz smanjeno učešće perifernih limfocita, kao i sa poremećajem reparativnih mehanizama [39]. Početak progresivnog toka bolesti korelira sa starenjem uslovljenim smanjenjem remijelinizacionog kapaciteta [40]. Kumulativno delovanje prethodno već opisanih mehanizama poput povećane degeneracije oligodendrocita, oksidativnog stresa, akumulacije gvožđa i mikroglijalne disfunkcije značajno ograničava remijelinizacioni kapacitet CNS-a u uslovima starenja. Pokazano je da se sa starenjem kod miševa smanjuje sposobnost neuralnih stem i progenitorskih ćelija da proliferišu i diferentuju, pri čemu epigenetske promene na nivou promotorskih regiona dovode do nishodne regulacije gena odgovornih za ove procese [41].

Starenje dovodi do strukturnih i funkcionalnih alteracija jonskih glutamatnih receptora, što je posebno izraženo kod *N*-metil-D-aspartat receptora (NMDAR), koji su eksprimirani kako na neuronima, tako i na ćelijama imunskog sistema [42,43]. S druge strane, kod pacijenata sa multiplom sklerozom pokazano je značajno povećanje nivoa glutamata [44]. U uslovima povišene koncentracije glutamata i starenjem izmenjene NMDAR signalizacije, može doći do slabljenja neuroprotektivnih mehanizama i povećanja rizika od glutatomom posredovane ekscitotoksičnosti. Primenom NMDAR antagonista u animalnom modelu multiple skleroze ostvaren je izraženiji terapijski efekat kod starih u odnosu na mlade jedinke, kako u pogledu kliničke slike, tako i u pogledu parametara oksidativnog stresa i antioksidativne zaštite moždanog tkiva [45].

Od neprocenljivog značaja je fokusiranje budućih istraživanja na razvoj terapijskih strategija usmerenih na delimičnu restauraciju remijelinizacionog kapaciteta kod starijih bolesnika sa multiplom sklerozom. Potencijalni pristupi obuhvataju farmakološku modulaci-

Physiological aging leads to iron accumulation in microglial cells. In patients with multiple sclerosis, demyelination releases iron from damaged oligodendrocytes and myelin, which is subsequently taken up by microglia and macrophages. As a result, iron accumulates in microglial cells, particularly at the edges of chronically active lesions. This iron deposition is associated with a proinflammatory microglial phenotype and increased synthesis of reactive oxygen species, contributing to chronic neuroinflammation and progressive neurodegeneration in elderly patients with multiple sclerosis [38].

## AGING-ASSOCIATED CHANGES IN REPARATIVE MECHANISMS IN MULTIPLE SCLEROSIS

The pathophysiological mechanisms underlying PIRA are associated with compartmentalization of the inflammatory process within the CNS, reduced participation of peripheral lymphocytes, and disruption of reparative mechanisms [39]. The onset of a progressive disease course is associated with aging, resulting from reduced remyelination capacity [40]. The cumulative effect of the mechanisms described above, such as increased oligodendrocyte degeneration, oxidative stress, iron accumulation, and microglial dysfunction, significantly limits CNS remyelination capacity under aging conditions. Studies in mice have shown that aging reduces the proliferative and differentiative capacity of neural stem and progenitor cells, with epigenetic changes at promoter regions consequently regulating the genes responsible for these processes [41].

Aging induces structural and functional alterations of ionic glutamate receptors, particularly pronounced in *N*-methyl-D-aspartate receptors (NMDARs), which are expressed on both neurons and immune cells [42,43]. Conversely, patients with multiple sclerosis exhibit a significant increase in glutamate levels [44]. Under conditions of elevated glutamate concentration and aging-altered NMDAR signaling, neuroprotective mechanisms may be weakened, increasing the risk of glutamate-mediated excitotoxicity. Using NMDAR antagonists in an animal model of multiple sclerosis, a more pronounced therapeutic effect was achieved in old compared to young individuals, both in terms of the clinical picture and in terms of parameters of oxidative stress and antioxidant protection of brain tissue [45].

It is of utmost importance to focus future research on developing therapeutic strategies aimed at partially restoring remyelination capacity in elderly patients with multiple sclerosis. Potential approaches include pharmacological modulation of the SASP profile and microglial activity to create a pro-regener-

ju SASP profila i aktivnosti mikroglije u cilju stvaranja pro-regenerativnog mikrookruženja [24], primenu lekova koji utiču na funkciju mitohondrija i smanjuju oksidativni stres u oligodendrocitima i njihovim prekursorima [46], korišćenje molekula koji podstiču proliferaciju i diferencijaciju neuralnih stem i progenitorskih ćelija [47], kao i ciljanje glutamatne signalizacije, uključujući upotrebu NMDAR antagonista [45], u selektovanim podgrupama starijih bolesnika. Ovakvi pristupi mogli bi da doprinesu očuvanju rezidualnog reparativnog potencijala CNS-a i uspore akumulaciju invaliditeta, a njihovu efikasnost i bezbednost trebalo bi sistematski ispitati u kliničkim studijama koje eksplicitno uključuju stariju populaciju bolesnika.

## ZAKLJUČAK

Poslednje dve decenije beleži se porast broja starijih pacijenata sa multiplom sklerozom, uključujući one kod kojih je bolest započela u mlađem životnom dobu (20-40 godina), kao i one sa kasnim početkom bolesti nakon 50. godine života. Proces starenja dovodi do značajnih promena imunskog i nervnog sistema, koje interaguju sa autoimunskim mehanizmom oštećenja CNS-a tokom multiple skleroze i doprinose transformaciji kliničkog toka u progresivni obrazac. Tokom vremena patofiziologija bolesti evoluira od aktivnih inflamatornih lezija ka hronično aktivnim, sporo ekspanzivnim lezijama koje karakteriše proinflamatorna mikroglija. Razumevanje uticaja starenja na molekularne i ćelijske mehanizme koji pokreću i održavaju bolest ključno je za primenu ciljanih terapija kod starijih bolesnika. Ova populacija bi trebalo da bude uključena u kliničke studije novih lekova, posebno onih koji modulišu aktivaciju mikroglije, poboljšavaju funkciju mitohondrija, pospešuju neuroprotekciju i remijelinizaciju ili antagonizuju NMDAR.

**Zahvalnica:** Ovaj rad finansiralo je Ministarstvo nauke, tehnološkog razvoja i inovacija Republike Srbije kroz dva ugovora sa Univerzitetom u Beogradu – Farmaceutskim fakultetom, broj 451-03-33/2026-03/200161 i broj 451-03-34/2026-03/200161.

**Sukob interesa:** Nije prijavljen.

active microenvironment [24], administration of drugs that enhance mitochondrial function and reduce oxidative stress in oligodendrocytes and their precursors [46], use of molecules that promote proliferation and differentiation of neural stem and progenitor cells [47], as well as targeting glutamate signaling, including the use of NMDAR antagonists [45], in selected subgroups of elderly patients. Such approaches could help preserve the residual reparative potential of the CNS and slow the accumulation of disability, and their effectiveness and safety should be systematically evaluated in clinical studies that explicitly include elderly patients.

## CONCLUSION

Over the past two decades, the number of elderly patients with multiple sclerosis has increased, including individuals whose disease began at a younger age (20–40 years) as well as those with late-onset disease after 50 years of age. Aging induces significant changes in the immune and nervous systems, which interact with the autoimmune mechanisms of CNS damage in multiple sclerosis and contribute to the transformation of the clinical course into a progressive pattern. Over time, the pathophysiology of multiple sclerosis evolves from active inflammatory lesions to chronically active, slowly expanding lesions characterized by proinflammatory microglia. Understanding the effects of aging on the molecular and cellular mechanisms that initiate and sustain the disease is crucial for applying targeted therapies in elderly patients. This population should be included in clinical trials of new drugs, particularly those that modulate microglial activation, enhance mitochondrial function, promote neuroprotection and remyelination, or antagonize NMDARs.

**Acknowledgement:** This work has been financed by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia through two contracts with the University of Belgrade Faculty of Pharmacy, number 451-03-33/2026-03/200161 and number 451-03-34/2026-03/200161.

**Conflict of interest:** None declared.

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