# Neurološke promjene u dugovječnosti

# */ Neurological Changes in Longevity*

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Učestalost neuroloških bolesti kao i njihovo breme postaju rastući problem kao rezultat starenja populacije. Neurološke bolesti povezane su s visokom smrtnošću, invaliditetom, institucionalizacijom i hospitalizacijom a broj ljudi koji boluju od neuroloških bolesti svakim danom sve više raste. Porast učestalosti onesposobljavajućih, neizlječivih neuroloških poremećaja ima poguban utjecaj na bolesnike, obitelji, ali i čitavo društvo, te traženje načina za usporenje njihove progresije i smanjenje učestalosti postaje imperativ. Starenje je povezano s nakupljanjem mnogih patoloških stanja, posebno cerebrovaskularne bolesti, ali i s pojavom neurodegeneracije. U česte neurološke poremećaja koji pogađaju stariju populaciju ubrajamo moždani udar, polineuropatiju, Alzheimerovu bolest i Parkinsonovu bolest. Samo Alzheimerova bolest zahvaća jednu trećinu osoba starijih od 85 godina te se očekuje da se broj oboljelih koji je u 2015. godini procijenjen na 40 milijuna poveća na 135 milijuna do 2050. godine. Svake godine 15 milijuna ljudi širom svijeta doživi moždani udar. Oko 6 milijuna tih ljudi umre u roku od jednog sata, a 5 milijuna bolesnika ostaje trajno onesposobljeno. Incidencija Parkinsonove bolesti raste s godinama i ne pokazuje pad ni u najstarijim dobnim skupinama. Polineuropatija se javlja u 5,5 % starije populacije, njezina prevalencija raste s dobi te je u skupini ispitanika starijih od 80 godina iznosila čak 13,2 %. Epilepsija se relativno češće javlja u starije populacije u usporedbi s djecom i odraslima, a njezina sve veća učestalost u starijih osoba povezana je s porastom različitih etiologija epileptogenih stanja koja mogu predstavljati terapijske ciljeve. Zbog vrhunca incidencije nakon 75. godine starenje globalne populacije u narednim će godinama također rezultirati velikim brojem bolesnika koji boluju od amiotrofične lateralne skleroze.

S obzirom na svjetski trend starenja populacije koji ima za posljedicu povećanu učestalost neuroloških bolesti prevencija i adekvatno zbrinjavanje neuroloških zbivanja postaju javnozdravstveno pitanje.

*/ Neurological diseases are becoming more prevalent as the world's population ages, and their burden is expected to increase globally. The number of people living with neurological conditions in the world is rising and will continue to increase. The increase in the frequency of disabling, currently incurable neurologic disorders is likely to have a devastating impact on individuals, families, and societies, unless effective means to reduce the incidence and progression of these diseases are discovered. Moreover, neurological diseases are associated with a high risk for adverse health outcomes, including mortality, disability, institutionalization, and hospitalization. Ageing is associated with accumulation of many pathologies, notably cerebrovascular disease, but also with the emergence of neurodegeneration. Some of the more common neurological disorders that affect older adults include stroke, polyneuropathy, Alzheimer's disease, and Parkinson's disease. Alzheimer's disease alone affects between one-third and one-half of people above 85 years of age; thus, the number of people affected, estimated at 40 million worldwide in 2015, is anticipated to increase to 135 million by 2050. Every year, 15 million people worldwide suffer a stroke. About 6 million of these people die within hours, and another 5 million are left disabled. The prevalence of Parkinson's disease increases with age, with no levelling off in the highest age categories. Polyneuropathy occurs in 5.5% of the elderly population and increases with age with a prevalence of 13.2% in the group of people over the age of 80. Epilepsy is comparatively more frequent in the older population compared with children and adults, and its increasing incidence in the elderly is related to the rise in age-related epileptogenic conditions with specific underlying pathophysiological mechanisms that may represent therapeutic targets. Because of a peak of*

*incidence around after 75 years of age, ageing of the global population will also result in a great increase in the number of patients suffering from amyotrophic lateral sclerosis in the coming years.*

*Since the aging population is a real public health issue, it is essential to identify the incidence and prevalence of neurologic diseases in the elderly population in order to develop strategies for prevention and management.*

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## UVOD

Starenje populacije je demografski fenomen s velikim posljedicama u različitim sektorima. Prema podatcima iz 2017. godine broj ljudi starijih od 60 godina do 2050. godine udvostručit će se od 962 milijuna u 2017. na 2,1 milijardu 2050. godine. Najstariji udio stanovništva koje predstavlja populacija starija od 80 godina u istom će se razdoblju utrostručiti sa 137 milijuna u 2017. na 425 milijuna 2050. godine (1). Starenje stanovništva rezultira snažnim porastom broja bolesnika, jer se očekuje da se učestalost većine bolesti povećava s dobi. Kako bi se te bolesti mogle pravodobno liječiti te potencijalno prevenirati, osnovno je otkriti njihove čimbenike rizika. Kao odgovor na ovaj problem koji je novonastao u svjetlu aktualnih demografskih promjena provedene su prospektivne studije praćenja zdrave populacije. Rezultati tih istraživanja su pokazali usku povezanost između životne dobi i učestalosti mnogih neuroloških poremećaja te nametnuli zaključak da je upravo neurologija medicinska disciplina na koju starenje stanovništva ima poseban utjecaj. Štoviše, neurološki i psihijatrijski poremećaji

## INTRODUCTION

The increase in the number of elderly people of the world population is an ongoing worldwide phenomenon with major implications in many different sectors. According to the World Population Prospects: the 2017 Revision, the number of people over 60 will more than double by 2050 – from 962 million in 2017 to 2.1 billion in 2050. The oldest segment of the population, that is, people over 80 years of age, is expected to triple over this period, from 137 million in 2017 to 425 million in 2050 (1). As a response to the demographic changes that lead to an increase of the proportion of elderly people in most populations, several prospective follow-up studies have been conducted. It is clear that the aging of the population will produce a strong rise in the number of elderly people living with diseases, as most diseases cluster at the end of life, and that to discover the causes of diseases in the elderly one would have to study risk factors of those diseases. Results showed that there is the close relationship between age and the incidence of many neurological disorders, and that neurology is a medical

bili su najvažniji uzroci invalidnosti u starijih osoba (2). Socioekonomski teret neuroloških bolesti naglo raste starenjem stanovništva i stalnim porastom očekivanog trajanja života širom svijeta te nedavna studija procjenjuje da globalni troškovi iznose više od 2 % svjetskog bruto društvenog proizvoda. Očekuje se da će se s obzirom na demografske promjene ovaj trend dalje nastaviti (3). Javno zdravstveni izvještaji Velike Britanije za 2018. godinu *"Neurology Mortality"* pokazao je trend porasta smrtnosti od neuroloških bolesti za 39 % tijekom 13 godina, dok je smrtnost populacije u istom razdoblju pala za 6 % (4). Kao posljedica navedenih promjena danas postoji tendencija da se neurološke bolesti proglase javno zdravstvenim prioritetima.

## NEUROLOŠKI POREMEĆAJI U STARIJOJ POPULACIJI

Starenje populacije rezultira povećanim brojem određenih neuroloških bolesti, ali pri tome ne treba izgubiti iz vida da učestalost pojedinih neuroloških zbivanja ne prati porast životne dobi. Neki od neuroloških poremećaja, poput glavobolje, uobičajeni su u populaciji tijekom života, ali se njihova učestalost ne povećava u starijoj životnoj dobi. Naprotiv, pojedina zbivanja poput migrene češća su u mlađoj životnoj dobi tako da bolesnica koja je imala učestale napade migrene u dobi iznad 60 godina može imati znatno rjeđe napade ili napadi mogu u potpunosti izostati. Starenje je povezano s nakupljanjem mnogih patologija, posebno u sklopu cerebrovaskularne bolesti, ali i s pojavom neurodegeneracije. Neki od češćih neuroloških poremećaja koji pogađaju starije osobe su moždani udar, polineuropatije, Alzheimerova i Parkinsonova bolest.

Svake godine 15 milijuna ljudi širom svijeta dobije moždani udar. Oko 6 milijuna ljudi s moždanim udarom umre u roku od jednog sata, a 5 milijuna ima trajni deficit. U Rotterdamskoj

discipline that will be particularly impacted by the ageing population. Moreover, neurological and psychiatric disorders were the most important causes of disability in the elderly (2). Recent estimates indicate that the global costs of neurologic illnesses total more than 2% of the annual world gross domestic product. This socioeconomic burden is expected to grow steeply with the ageing of populations and continuing increase in life expectancy worldwide (3). England's 2018 public health Neurology Mortality reports show that the number of deaths in England related to neurological disorders rose by 39% over 13 years, while deaths in the general population fell by 6% over the same period (4). As a result, this has led to widespread calls for declaring these diseases a global health priority.

## TYPE OF NEUROLOGICAL DISORDER COMMON IN ELDERLY POPULATION

Accelerated ageing will be accompanied by a rise in the number of patients affected by certain neurological disease, but not all neurological conditions rise with advanced age. Some neurological disorders, such as headache, are common in the global population during the course of life but are not frequently encountered in the population of the elderly. Ageing is associated with accumulation of many pathologies, notably cerebrovascular disease, but also with the emergence of neurodegeneration. Some of the more common neurological disorders that affect older adults include stroke, polyneuropathy, Alzheimer's disease, and Parkinson's disease.

Every year, 15 million people worldwide have a stroke. About 6 million of these people die within hours, and another 5 million are left disabled. In a Rotterdam study, which included 6.844 participants who were over 55 years of age and free from stroke that during the study, showed that 1.020 strokes occurred among the

studiji u kojoj je praćeno 6.844 sudionika starijih od 55 godina i bez znakova moždanog udara tijekom praćenja, 1.020 osoba je razvilo moždani udar (5). Analiza registra moždanih udara Dijon pokazala je da će do 2030. godine doći do očekivanog porasta ukupnog broja slučajeva moždanog udara za 55 %, pri čemu će ovo povećanje uvelike utjecati na porast slučajeva koji pogađaju starije osobe (65 %-tna učestalost u populaciji starijoj od 75 godina u odnosu na 25 %-tnu učestalost u ljudi mlađih od 75 godina), što ima velike posljedice u pogledu buduće organizacije zdravstvene skrbi i potrebe za resursima (6).

U današnjim društvima koja su obilježena starenjem populacije demencija je jedan od glavnih zdravstvenih problema. Učestalost demencije je visoka kod starijih osoba i to posebno u populaciji vrlo starih ljudi. Dosadašnja istraživanja su pokazala da je 9 % ispitanika u dobi od 65 godina i više dementno za razliku od 34 %, ako se gleda životna dob od 85 i više godina. Od svih slučajeva demencije 72 % bilo je uzrokovano Alzheimerovom bolešću. Iz dosadašnjih rezultata se neminovno nameće zaključak da je izražen porast prevalencije demencije s godinama posljedica značajnog porasta Alzheimerove bolesti. Rezultati velike EURODEM studije kojom je obuhvaćeno čak 28.768 osoba dokazali su da učestalost demencije i Alzheimerove bolesti ne prestaje rasti s dobi te se i dalje povećava u populaciji ljudi u dobi od 85 do 90 godina (7-9).

Učestalost Parkinsonove bolesti, druge po učestalosti neurodegenerativne bolesti, povećava se s dobi, prateći isti trend i u najvišim dobnim kategorijama i bez značajnih spolnih razlika. Podatci o prevalenciji prema objavljenoj epidemiološkoj studiji bili su 0,3 % za one u dobi od 55 do 64 godine, 1,0 % za skupinu u dobi od 65 do 74 godine, 3,1 % za skupinu od 75 do 84 godine, i 4,3 % za skupinu od 85 do 94 godina. U najstarijoj skupini između 95 do 99 godina prevalencija je bila 5,0 % (10).

participants (5). Analysis of the Dijon Stroke Registry demonstrated that there "will be an anticipated 55% increase in the total annual number of stroke cases by 2030, this increase being largely driven by a rise in cases affecting elderly people (65% in people ≥75 years old versus 25% in those < 75 years old), with major implications in terms of future care organization and resource needs" (6).

Dementia is one of the major health problems in aging societies. Dementing disorders are common in elderly and, especially, very old people. According to existing studies, 9% of subjects aged 65 and above and 34% of subjects aged 85 and over had dementia. Of all cases of dementia, 72% were cases of Alzheimer's disease. It was concluded that the pronounced increase in the prevalence of dementia with age was due to a substantial increase in Alzheimer's disease. The EURODEM study that included 28.768 person found that the incidence of dementia and Alzheimer's disease does not cease to increase with age and continues to increase in the population aged between 85 and 90 (7-9).

The prevalence of Parkinson' disease increased with age with no levelling off in the highest age categories and no significant gender difference. According to a published epidemiological study, the prevalence figures "were 0.3% for those aged 55 to 64 years, 1.0% for those 65 to 74, 3.1% for those 75 to 84, and 4.3% for those 85 to 94" and among "95- to 99-year-old women the prevalence was 5.0%" (10).

Polyneuropathy occurs in 5.5% of the elderly population and increases with age. The results of the study clearly showed that when investigating those over the age of 80, 13.2% of participants had polyneuropathy. Almost half of the cases were newly diagnosed, indicating that the presence of polyneuropathy is underreported or underdiagnosed in almost half of these persons (11).

Epilepsy is comparatively more frequent in the older population when compared with children

Polineuropatija se javlja s prevalencijom od 5,5 % u starijoj populacije s trendom povećanja starenjem te u skupini ispitanika starijih od 80 godina prevalencija je bila čak 13,2 %. Ista studija je također dokazala da je gotovo polovica slučajeva bila novo dijagnosticirana, što ukazuje da je prisutnost polineuropatije u gotovo velikom broju populacije neprepoznata i nedijagnosticirana (11).

Učestalost epilepsija je relativno veća u starijoj populaciji u usporedbi s djecom i odraslima. Sve veća učestalost epilepsije u starijih osoba povezana je s porastom različitih etiologija čija učestalost raste s dobi (12). Zbog vrhunca incidencije nakon 75. godine, starenje globalne populacije u narednim će godinama također rezultati velikim brojem bolesnika koji boluju od amiotrofične lateralne skleroze (13).

Neurološka zbivanja dijele mnoge čimbenike rizika te vrlo često bolesnik s jednim neurološkim zbivanjem tijekom vremena razvija i drugo neurološko zbivanje. Bolesnici koji boluju od moždanog udara imaju povećani rizik za demenciju, bolesnici koji boluju od demencije imaju povećani rizik za moždani udar, što potvrđuje *Framingham Heart* studija. Pojava jedne bolesti (npr. moždani udar) uzrokuje razvoj etiologije kao posljedice primarnog uzroka (npr. demencije nakon moždanog udara). Osim navedenog pojedini čimbenici rizika (npr. hipertenzija) nisu povezani samo s povećanom učestalošću neuroloških bolesti već i s povećanim mortalitetom od drugih uzroka (npr. srčanih bolesti) (14).

## POSEBNOSTI NEUROLOŠKIH BOLESTI U STARIJIH OSOBA

Kliničari trebaju biti upućeni u posebnosti neuroloških bolesti u starijih osoba uključujući različite kliničke manifestacije, specifične uzroke i prilagođeni terapijski pristup. Starenje samo po sebi nije bolesno stanje, ali može biti u inter-

and adults, and its increasing incidence in the elderly is related to the rise in age-related epileptogenic conditions with specific underlying pathophysiological mechanisms that may represent therapeutic targets (12). Because of a peak of incidence around after 75 years of age, ageing of the global population will also increase the number of patients suffering from amyotrophic lateral sclerosis in coming years (13).

These common neurological diseases share many risk factors and subsequently tend to show substantial co-occurrence, with stroke and parkinsonism patients at increased risk of dementia, and patients with dementia at increased risk of stroke. Framingham Heart Study reported lifetime risks of both dementia (1 in 5 women, 1 in 10 men) and stroke (1 in 5 women, 1 in 6 men). The occurrence of one disease (e.g. stroke) causes the development of etiology as a consequence of primary stroke (e.g. post stroke dementia). Similarly, several risk factors (e.g. hypertension) increase the susceptibility for common neurological diseases and are associated with an increased risk of dying from other causes (e.g. heart disease) (14).

## PARTICULARITIES OF NEUROLOGICAL DISEASES IN THE ELDERLY

Clinicians should be aware of some particularities of neurological diseases in the elderly, including different clinical manifestations, specific underlying causes, and tailored management of treatments. Age by itself is not a disease condition but may interact with several aspects of neurological diseases including incidence, clinical expression, or natural evolution. In the case of some neurologic conditions that are present throughout life and remain frequent in the elderly, there is insufficient data about therapeutic approaches in advanced age since most older patients are excluded from large tri-

akciji s nekoliko aspekata neuroloških bolesti, uključujući incidenciju, klinički fenotip i progresiju. O nekim neurološkim stanjima koja su prisutna tijekom života i koja su česta kod starijih osoba nema dovoljno podataka o terapijskom pristupu u starijoj dobi, jer je većina starijih bolesnika isključena iz velikih ispitivanja i često imaju više komorbiditeta i polifarmacije. Ostala neurološka stanja su izraziti klinički fenotip u starijoj dobi i stoga predstavljaju terapijski izazov.

Komorbiditeti u starijih osoba su pravilo, a ne iznimka. Veliko nacionalno istraživanje zdravlja i razvoja u Velikoj Britanije uključilo je u istraživanje osobe rođene 1946. godine i slijedilo ih prospektivno. Rezultati su pokazali da ljudi i u dobi od 60 do 64 godine imaju u prosjeku dvije bolesti: 54 % ih ima hipertenziju, 31 % pretilost, 26 % hiperkolesterolemiju i 25 % dijabetes melitus ili smanjenu toleranciju glukoze. S druge strane, samo 15 % osoba nije imalo komorbiditeta. U neselektiranom uzorku pojedinaca starijih od 85 godina učestalost hipertenzije, osteoartritisa, ateroskleroze i katarakte bila je oko 50 %, a otprilike je 90 % ispitanika imalo tri ili više bolesti (15).

## MOGU LI SE SPRIJEČITI NEUROLOŠKI POREMEĆAJI?

Broj bolesnika koji boluju od neuroloških poremećaja kao i posljedično opterećenje zdravstvenog sustava povezano je s dva demografska fenomena: starenje i porast broja stanovnika. Stoga je ključno razviti strategije za njihovu prevenciju (16). Prvi korak je kontrola čimbenika rizika poput pušenja, visokog krvnog tlaka, visokog kolesterola, pretilosti i nedostatka tjelovježbe koja može pridonijeti moždanom udaru i eventualno drugim neurološkim problemima. Posljednjih godina postalo je jasno da su kardiovaskularni čimbenici rizika i niska edukacija također čimbenici rizika za razvoj demencije. Rezultati prospektivne Roterdam-

als and often have multiple comorbidities and polypharmacy. Other neurologic conditions present with a distinct clinical phenotype in older age and therefore represent a therapeutic challenge.

Comorbidities in elderly people are the rule rather than the exception. Thus, in the MRC National Survey of Health and Development, a representative UK sample included those born in 1946 and followed them prospectively. Results showed that by the age of 60–64 the participants had on average two medical conditions: 54% had hypertension, 31% obesity, 26% hypercholesterolemia, and 25% either diabetes mellitus or impaired glucose tolerance. By contrast, only 15% were free from any comorbidity. In an unselected sample of individuals over the age of 85, the prevalence of hypertension, osteoarthritis, atherosclerosis, and cataract were each around 50%, and ~90% had three or more conditions (15).

## CAN NEUROLOGICAL DISORDERS BE PREVENTED?

In terms of absolute number of people affected by neurological disorders, most of the increase in the burden of neurological diseases was associated with ageing of the population and population growth. Therefore, it is essential to develop strategies for their prevention (16). The first step is controlling risk factors such as smoking, high blood pressure, high cholesterol, obesity, and lack of exercise, which can contribute to stroke, and possibly other neurological issues. In recent years, it has become clear that cardiovascular factors and low education are risk factors of dementia. The results of the prospective Rotterdam study showed that about one quarter to one third of dementia cases could potentially be prevented through optimal prevention or treatment of cardiovascular risk factors and diseases and the improvement of the educational level (17). As advocated by the recent

ske studije su dokazali da se oko četvrtine do jedne trećine slučajeva demencije potencijalno može spriječiti optimalnom prevencijom ili liječenjem kardiovaskularnih čimbenika rizika i poboljšanjem obrazovne razine (17). Prema nedavno objavljenom svjetskom izvještaju o Alzheimerovoj bolesti, većina tih čimbenika potencijalno se može modificirati, što pruža mogućnost za prevenciju demencije (18). Podatci iz Roterdamske studije su pokazali da se oko polovine slučajeva moždanog udara u populaciji može pripisati kombinaciji nekoliko etioloških čimbenika: hipertenziji, pušenju, dijabetesu, fibrilaciji atrija, srčanim bolestima i prekomjernoj težini / pretilosti. Autori su zaključili da se većina moždanih udara može pripisati utvrđenim etiološkim faktorima koji se mogu modificirati i da bi se teorijski mogla smanjiti učestalost moždanih udara uklanjanjem tih čimbenika rizika u populaciji (19).

Rezultati prospektivnih studija pokazuju da preventivne strategije koje odgađaju nastanak moždanog udara, demencije i Parkinsonove bolesti za 1 do 3 godine mogu smanjiti učestalost ovih stanja za 20 – 50 %. Ovi rezultati idu u prilog važnosti prevencije kako bi se smanjio trenutni i budući pobol neuroloških bolesti u starijoj populaciji (20).

Nedavna velika studija pokazala je pad u trendu incidencije demencije u stanovništvu koje živi u zemljama s visokim dohotkom što je protumačeno kao početni rezultat preventivnih strategija. Ovo nameće zaključak da je boljom kontrolom vaskularnih čimbenika rizika, poboljšanjem obrazovanja kao i drugim mjerama u okviru javnog zdravstva smanjena prevalencija demencije (21).

## ZAKLJUČAK

Produženi životni vijek i porast udjela starije populacije je demografski fenomen posljednjih godina prisutan širom svijeta zbog čega sve

World Alzheimer report, most of these factors are potentially modifiable, which provides an opportunity for prevention of dementia (18). Data from the Rotterdam study found that about half of the strokes in the study population were attributable to a combination of several etiological factors: hypertension, smoking, diabetes, atrial fibrillation, heart disease, and excess weight/obesity. Authors concluded that the majority of the strokes were attributable to established modifiable etiological factors and could theoretically be prevented by eliminating these risk factors from the population (19).

Prospective studies that were designed to investigate the causes and consequences of long-term and disabling diseases in the elderly suggested that preventive strategies that delay disease onset of stroke, dementia, and Parkinson's disease by 1–3 years have the potential to reduce these risks by 20–50%. These findings strengthen the call for a focus on prevention to reduce the current and projected burden of common neurological diseases in the ageing population (20).

Recent observations on declining dementia incidence trends from several large population-based studies in high-income countries may in fact reflect the (initial) signs of these preventive strategies through better vascular risk factor management, improved educational attainment, or other public health developments that improved the resilience for dementia (21).

## CONCLUSION

Increasing life expectancy and population growth worldwide in recent years mean that more people are now reaching the age in which neurological disorders are most prevalent. Consequently, neurological disorders are a large cause of disability and death worldwide. Globally, the burden of neurological disorders has increased substantially over the past 25

veći broj ljudi doseže dob u kojoj su neurološki poremećaji česti. Posljedično su neurološki poremećaji značajan uzrok invaliditeta i mortaliteta diljem svijeta. Kako bi se spriječilo daljnji porast invaliditeta i mortaliteta bitno je senzibilizirati javnost za prepoznavanje različitih neuroloških stanja te nastojati provoditi mjere prevencije neuroloških bolesti.

years because of population ageing. Raising awareness and informing the public about the lifetime risk of neurological disorders should be encouraged. Preventive measures for the prevention of neurological diseases should be tailored to individual lifetime risk estimates to successfully develop a future prevention programme for common neurological diseases.

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