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ALCHAJMEROVA BOLEST: EPIDEMIOLOŠKE KARAKTERISTIKE I PREVENCIJA

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SAŽETAK

Alchajmerova bolest (AB) je progresivna neurodegenerativna bolest mozga koja predstavlja veliki javnozdravstveni izazov. U svetu, prema podacima za 2018. godinu, procenjen broj ljudi koji živi sa AB je bio najmanje 50 miliona. U Sjedinjenim Američkim Državama (SAD), prema podacima za 2021. godinu, čak 6,2 miliona ljudi uzrasta 65 i više godina živi sa AB. U poslednjih 20 godina, AB se 145,2% češće prijavljuje kao uzrok smrti, delom zbog toga što se uzrok smrti preciznije utvrđuje, a najviše zbog toga što je učestalost AB sve veća usled starenja populacije. Na osnovu broja izgubljenih godina „zdravog" života (engl. *Years of Life Lost* - YLL) AB je četvrti, a prema izgubljenim godinama života sa nesposobnošću određene težine i trajanja (engl. *Years of Life with Disability* - YLD) devetnaesti, a prema zbirnom indikatoru DALY-ju (godine života korigovane u odnosu na nesposobnost, engl. *Disability Adjusted Life Years* - DALY) šesti vodeći uzrok opterećenja američke populacije bolestima u 2016. godini. Nemodifikujući faktori rizika za nastanak AB su starosna dob, genetika, pozitivna porodična istorija, dok su modifikujući faktori rizika pušenje, dijabetes, gojaznost u srednjoj životnoj dobi, hipertenzija, prehipertenzija, povišene vrednosti holesterola, nedovoljna fizička aktivnost, nezdrava ishrana, kraće formalno obrazovanje, nizak nivo mentalne stimulacije na poslu, trauma mozga, loš san, zloupotreba alkohola i oštećenje sluha. Procenjuje se da se redukcijom modifikujućih faktora rizika može sprečiti ili odložiti 40% slučajeva Alchajmerove demencije (AD). Biomarkeri koji mogu da se koriste u cilju identifikovanja ove bolesti su beta-amiloidni protein koji formira beta-amiloidni plak, abnormalni tau protein koji se akumulira u neuronima, i postojanje inflamacije i atrofije mozga. Dok čekamo da istraživači pronađu lek za ovu bolest, važno je podizati svest o dostupnim skrining metodama za rano otkrivanje AB, kao i o mogućnostima prevencije.

Ključne reči: Alchajmerova bolest, epidemiologija, prevalencija, mortalitet, faktori rizika, biomarkeri

Uvod

Alchajmerova bolest (AB) je progresivna neurodegenerativna bolest mozga. Početak oboljenja može da se javi do 20 godina pre pojave simptoma. U početku, promene mozga su previše male da bi ih obolela osoba mogla primetiti simptome. Međutim, broj oštećenih i uništenih neurona se povećava tokom vremena, što dovodi do prvih simptoma kao što su gubitak pamćenja i poremećaj govora. Kasnije, osoba gubi sposobnost da obavlja osnovne telesne funkcije, postaje vezana za krevet uz neophodnost stalne nege, i na kraju umire.

U svetu, prema podacima za 2018. godinu, procenjen broj ljudi koji živi sa AB je bio najmanje 50 miliona (1). U Sjedinjenim Američkim Državama (SAD), prema podacima za 2021. godinu, čak 6,2 miliona ljudi uzrasta 65 i više godina živi sa AB (2). Takođe, predviđa se da će ovi brojevi dalje rasti sa povećanjem prosečne starosti stanovništva. Kada se uzmu u obzir veliki finansijski troškovi lečenja i nege pacijenata obolelih od AB, koji su procenjeni na jedan trilion američkih dolara 2018. godine (2), postaje očigledno da je AB veliki javnozdravstveni problem. Dok čekamo da istraživači naprave pomak prema pronalasku leka, važno je podizati svest o trenutno dostupnim metodama skrininga za rano otkrivanje AB i najčešćim faktorima rizika za ovo obolevanje, kao i o tome šta je moguće uraditi da bi se oni redukovali ili eliminisali.

Obolevanje

Prevalencija je proporcija, odnosno deo populacije sa oboljenjem (bez obzira kada je bolest nastala) u bilo kojoj tački vremena, dok je godišnja stopa incidencije broj novoobolelih tokom date

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ALZHEIMERS's DISEASE: EPIDEMIOLOGICAL CHARACTERISTICS AND ITS PREVENTION

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SUMMARY

Alzheimer's disease is a progressive neurodegenerative brain disease that is of immense public health interest. Worldwide, according to data from 2018, the approximated number of people living with Alzheimer's was at a minimum 50 million. In the United States, according to data from 2021, there were as many as 6.2 million people age 65 and over living with Alzheimer's. In the last 20 years, Alzheimer's disease is being recorded 145.2% more frequently as the cause of death, partially due to the cause of death being more accurately attributed, but mostly due to the growing frequency of Alzheimer's disease due to the aging of the population. Based on years of life lost(YLL), Alzheimer's disease was the fourth, according to years of life with disability (YLD) nineteenth and according to the sum indicator DALY (Disability Adjusted Life Years) sixth leading cause of burden amongst diseases in the USA in 2016. The nonmodifiable risk factors for developing Alzheimer's disease are age, genetics, and family history, while the modifiable risk factors are smoking, diabetes, midlife obesity, hypertension, prehypertension, high cholesterol, insufficient physical activity, unhealthy diet, shorter length of formal education, low level of mental stimulation at work, traumatic brain injury, poor sleep, alcohol abuse, and hearing impairment. It is estimated that by reducing the modifiable risk factors, 40% of cases of Alzheimer's dementia can be prevented or postponed. The biomarkers that can be used for early detection of this disease are beta-amyloid protein that forms beta-amyloid plaques, abnormal tau protein accumulated inside neurons, the existence of brain inflammation and atrophy. While we wait for researchers to find a cure for this illness, it is important to raise awareness of available screening methods for early detection of Alzheimer's disease and prevention opportunities.

Keywords: Alzheimers disease, epidemiology, prevalence, mortality, risk factors, biomarkers

Introduction

Alzheimer's disease is a progressive neurodegenerative brain disease. The disease's onset may occur up to 20 years before any symptoms appear. In the beginning, the brain changes are too small for the diseased individual to notice. However, the number of damaged and destroyed neurons grows over time, leading to the first symptoms like memory loss and speech impairment. Later, the person loses the ability to perform basic bodily functions, becomes bed-bound in need of permanent care, and finally passes away.

Worldwide, according to data from 2018, the approximated number of people living with Alzheimer's was at a minimum 50 million (1). In the United States, according to data from 2021, there were as many as 6.2 million people age 65 and over living with Alzheimer's (2). Furthermore, these numbers are projected to continue growing with the increase of the population's average age. When the high financial costs of treatment and caretaking of Alzheimer's patients, which were estimated to be 1 trillion USD worldwide in 2018 (2), are taken into account, it becomes apparent that Alzheimer's disease is of immense public health interest. While we wait for researchers to make progress towards finding a cure, it is important to raise awareness of currently available early detection screening methods for Alzheimer's disease and the most common risk factors for developing this illness, and what can be done to reduce or eliminate them.

godine u odnosu na broj stanovnika sredinom posmatrane godine. S obzirom da se vrlo retko dešava da ljudi mlađi od 65 godina obole od Alchajmerove demencije (AD), studije se uglavnom fokusiraju na starije uzraste.

U SAD, broj osoba sa svim demencijama, uključujući i Alchajmerovu, će nastaviti da raste zajedno sa brzim porastom broja stanovnika uzrasta 65 i više godina, a predviđa se da će ih u SAD biti 88 miliona do 2050. godine (2,3). Više od 11,3% Amerikanaca starijih od 65 godina imaju AD (4,5). Procenjuje se da je broj prevalentnih slučajeva ove bolesti 6,2 miliona na osnovu studije u kojoj su korišćeni klinički simptomi demencije. Dokazi koji su dobijeni u studijama koje su bile bazirane na biomarkerima, pokazuju da je kod mnogih ljudi postavljena neadekvatna dijagnoza AD (6,7). Ove studije su utvrdile da je na osnovu simptoma kod 15-30% osoba bila postavljena pogrešna dijagnoza AD, odnosno to su bila lica sa demencijom uzrokovanom nekim drugim oboljenjem ili poremećajem. Osim toga, naučnici su već duže vreme svesni činjenice da blago kognitivno oštećenje predstavlja početnu fazu kroz koju svi pacijenti oboleli od demencije moraju da prođu. Sa napredovanjem znanja o biomarkerima i dijagnostike, moguće je odrediti koji slučajevi blagog kognitivnog oštećenja su izazvani AB i dodati ove slučajeve broju osoba koje su obolele od AB.

Ako se pretpostavi da trenutno 30% osoba sa AD nema ovu bolest, to znači da u SAD ostaje 4 miliona osoba starih 65 i više godina koje su obolele od AD. U jednom sistematskom preglednom radu utvrđeno je da 16,6% osoba starih 65 i više godina ima blago kognitivno oštećenje (8). Studije o biomarkerima sa PET skenerom su pokazale da polovina ljudi sa blagim kognitivnim oštećenjem ima specifične promene na mozgu povezane sa AB (9,10). 16,6% osoba sa blagim kognitivnim oštećenjem u starosnoj grupi 65 i više godina, je otprilike 10 miliona, polovina od toga, dakle 5 miliona ima blago kognitivno oštećenje zbog Alchajmera, što znači da kada dodamo taj broj broju od 4 miliona slučajeva AD, dobijamo da oko 9 miliona ljudi ima AB u SAD. Neophodno je sprovesti populacione studije bazirane na upotrebi biomarkera radi verifikovanja ove procene.

Incidencija AB raste sa godinama i iznosi 0,4% u starosnoj grupi 56-74 godine, 3,2% u grupi 75-84 godina, i 7,6% kod osoba starijih od 85 godina (11). Zbog stalno rastućeg broja ljudi starih 65 i više godina u SAD, predviđa se da će se godišnji broj novoobolelih od AD i drugih demencija udvostručiti do 2050. godine (12).

Pokazano je da je životni rizik od AB u 45. godini dva puta viši kod žena nego kod muškaraca (1 od 5 za žene u poređenju sa 1 od 10 za muškarce), a ovaj rizik dalje raste posle 65 godine kod oba pola (13). Otprilike dve trećine osoba sa AD su žene, odnosno 3,8 miliona u odnosu na 6,2 miliona slučajeva (14). Međutim, 3,8 miliona žena i 2,4 miliona muškaraca čine 12%, odnosno 9% populacije koja je starija od 65 godina u odnosu na pol (15), što daje temelj teoriji da s obzirom da je starost glavni faktor rizika za AB, žene imaju veći životni rizik za AB jer duže žive. Druga moguća objašnjenja se baziraju na rodnim razlikama po pitanju obrazovanja, zanimanja i zdravstvenog ponašanja, i biološkim razlikama među polovima. Takvi primeri su gori uslovi obrazovanja za žene rođene u prvoj polovini 20. veka (16) i rodna razlika u profesionalnim postignućima. Nedavno je pokazano kako su žene koje su radile u ranijim fazama života imale bolje kognitivne ishode kasnije tokom života (17).

Kada su u pitanju biološke razlike među polovima, brojne studije ukazuju da APOE-e4 genotip utiče na to da žene više obolevaju od AD (18,19) i neurodegenerativnih oboljenja (20) nego muškarci. Slična je povezanost uzmeđu APOE i AD kod oba pola, ali e4 genotip je opasniji za žene u određenim starosnim dobima (21). Tau i beta amiloidni proteini su opasniji za žene s obzirom da isti nivoi izazivaju neurodegeneraciju i kognitivni pad brže kod žena nego kod muškaraca.

Nedavno objavljeni rezultati studija pokazuju da rizik od demencije blago opada u SAD i drugim zemljama sa visokim dohotkom (22-24). Međutim, broj ljudi sa demencijom će nastaviti da raste zbog porasta prosečne starosti stanovništva. Takođe, očekuje se da će 68% globalne prevalencije demencije do 2050. godine biti u zemljama sa niskim ili srednjim prihodima za koje ne postoje dokazi za smanjenje rizika od demencije (25).

Umiranje

U SAD AB je vodeći uzrok umiranja kako među osobama uzrasta 65 i više godina (zauzima peto mesto), tako i u celokupnoj populaciji (zauzima šesto mesto) (26). Najteži oblici AB često izazivaju ozbiljne komplikacije kao što su nepokretnost ili pneumonija, a pneumonija predstavlja najčešći

Morbidity

Prevalence is the proportion, meaning the part of the population with the disease (regardless of when the disease occurred) at any point in time, while the annual incidence rate is the number of new cases during a given year in relation to the population in the middle of the observed year. As it is quite rare for individuals under the age of 65 to develop Alzheimer's dementia, the studies primarily focus on older demographics.

In the USA, the number of individuals with all types of dementia, including Alzheimer's, will continue rapidly increasing along with the rapid increase of the population age 65 and older, which is projected to be 88 million in the United States by 2050 (2,3). Over 11.3% of Americans age 65 and older have Alzheimer's dementia (4,5). It is estimated that the number of prevalent cases of this disease is 6.2 million, based on a study that used clinical symptoms of dementia. Evidence obtained in biomarker-based studies showed that many people were inadequately diagnosed with Alzheimer's dementia (6-7). These studies found that based on symptoms, 15-30% of individuals were incorrectly diagnosed with Alzheimer's dementia, that is, those were individuals with dementia caused by a different disease or disorder. Additionally, for a long time, scientists have been aware that mild cognitive impairment (MCI) is a precursor stage through which all dementia patients pass through. With the improvements in knowledge of biomarkers and diagnostics, it is possible to determine which MCI cases are caused by Alzheimer's and add those cases to the number of individuals diseased from Alzheimer's.

If it is supposed that 30% of the current individuals with Alzheimer's dementia do not have this disease, that means that in the United States, there are 4 million individuals age 65 or older left with Alzheimer's dementia. It was determined in a systematic review that 16.6% of individuals age 65 and older have mild cognitive impairment (8). Biomarker studies with PET scans showed that half of the people with mild cognitive impairment have brain changes linked to Alzheimer's disease (9,10). 16.6% of individuals with mild cognitive impairment in the age group 65 or older is roughly 10 million, so 5 million have mild cognitive impairment due to Alzheimer's, meaning that when we add that number to the 4 million Alzheimer's dementia cases, we get a rough estimate of 9 million individuals with Alzheimer's in the USA. It is necessary to conduct population-based biomarker studies to verify this estimate.

Alzheimer's incidence is greatly increased with age and amounts 0.4% in individuals 56-74, 3.2% in individuals 75-84, and 7.6% in individuals age 85 or older (11). Due to the ever-growing number of individuals age 65 and older in the USA, the yearly new cases of Alzheimer's and other dementias are expected to double by 2050. (12)

It was shown that the estimated lifetime risk of Alzheimer's dementia at age 45 was twice as high in women than in men (1 in 5 for women compared to 1 in 10 for men), and these risks further increase for both sexes at age 65 (13). Approximately two-thirds of individuals with Alzheimer's dementia are women, representing 3.8 million out of 6.2 million cases (14). However, the 3.8 million women and 2.4 million men represent 12% and 9% of their genders respective population age 65 or older (15) which lays the foundations for the theory that since age is the main risk factor for Alzheimer's, women have a higher lifetime risk for Alzheimer's because they live longer. Other possible explanations are based on gender differences in education, occupation and health behaviors, and biological differences between the sexes. Such examples are worse education conditions of women born in the first half of the 20th century (16) and a difference in occupational attainment between the genders. It was recently shown that females that participate in the workforce in the earlier stages of their lives had better outcomes in their cognition later in life (17).

In regards to biological sex differences, multiple studies suggest that APOE-e4 genotype impacts women towards developing Alzheimer's dementia (18,19) and neurodegeneration (20) stronger than men. The associations between APOE and Alzheimer's dementia are similar for both genders, but the e4 genotype is more dangerous for women in particular age ranges (21). Tau and beta-amyloid are more dangerous for women as the same levels cause neurodegeneration and cognitive decline faster in women than in men.

Some recent findings show that the risk of dementia has been decreasing slightly in the USA and other high-income countries (22-24). However, the number of people with dementia will continue growing due to the increase in the average age of

neposredni uzrok smrti kod osoba obolelih od AD (27). Kao i mnoga druga akutna stanja, pneumonija se često navodi kao primarni uzrok smrti kod osoba sa AB (28), što rezultira nemogućnošću da se odredi stvarni broj smrti izazvanih AB. Nedavno je objavljeno u jednoj studiji da je samo 5% od ukupno 14% smrtnih ishoda kod Amerikanaca starijih od 70 adekvatno pripisano demenciji na potvrdama o uzroku smrti za period 2000-2009. godine (29). Međutim, još je komplikovanije pravilno odrediti da je uzrok smrti AB zato što otprilike 15-30% osoba kod kojih je postavljena dijagnoza AD ima demenciju zbog nekog drugog uzroka (7,8).

U poslednjih 20 godina, AB je kao prijavljeni uzrok smrti porasla za 145,2%, što je rezultat toga da se uzrok smrti češće pravilno pripisuje ovoj bolesti i što je ona češće uzrok smrti zbog starenja populacije (26). U proseku, osobe sa dijagnozom AD preživljavaju 4 do 8 godina, i žive sa njom čak do 20 godina u retkim slučajevima (30). Stoga se procenjuje da dve trećine umrlih od demencije umre u domovima za stara lica (31).

Na osnovu broja izgubljenih godina "zdravog" života (engl. *Years of Life Lost* - YLL) AB je četvrti, a prema izgubljenim godinama života sa nesposobnošću određene težine i trajanja (engl. *Years of Life with Disability* - YLD) devetnaesti, a prema zbirnom indikatoru DALY-ju (godine života korigovanih u odnosu na nesposobnost, engl. *Disability Adjusted Life Years* - DALY) šesti vodeći uzrok opterećenja američke populacije bolestima u 2016. godini (32).

Faktori rizika

Kasna manifestacija AB, odnosno manifestacija bolesti kod osoba starih 65 i više godina, predstavlja najčešći oblik AB. Veruje se da je ova bolest rezultat multiplih faktora, a ne samo jednog faktora. Nemodifikujući faktori rizika za AB su uzrast, genetika, i porodična istorija. Ovi nemodifikujući faktori su takođe najvažniji faktori rizika za kasniju manifestaciju AB. Uzrast predstavlja najznačajniji faktor s obzirom da procenat ljudi koji obolevaju od AD u velikoj meri raste sa starenjem. U SAD, samo 5,3% osoba u uzrasnoj grupi 65-75 godina ima AD; postoji značajan porast od 13,8% u starosnoj grupi 75-84 godine, i 34,6% kod osoba starijih od 85 godina sa ovim tipom demencije (5). Važno je zapamtiti da AD nije normalan deo procesa starenja i da godine nisu dovoljan razlog za obolevanje od AD (33).

Pronađeno je više gena koji povećavaju rizik od obolevanja, a najviše se ističe APOE-e4 gen, s obzirom da ima najviše uticaja na kasniji početak AB. Ovaj gen kodira jedan od proteina nosača holesterola u krvotoku, i svi ljudi nasleđuju jedan od tri alela ovog gena od svakog roditelja. Aleli su e2, e3, i e4 tako da ima šest mogućih kombinacija alela. Oblik e4 povećava rizik u poređenju sa e3, dok e2 smanjuje rizik u poređenju sa oblikom e3. Na primer, osobe sa e4/e3 ili e4/e2 imaju tri puta veći rizik od obolevanja od AB od ljudi sa e3/e3 oblikom, dok osobe sa e4/e4 oblikom imaju 8-12 puta veći rizik od obolevanja od ljudi sa e3/e3 kombinacijom (34-36). Ovo se najverovatnije dešava zato što osobe sa e4 oblikom imaju veće šanse za beta-amiloidnu akumulaciju u ranijoj životnoj dobi od ljudi sa druga dva alela (37).

Porodična istorija AB nije neophodna da bi se obolelo od ove bolesti, ali ako neko ima rođaka iz najbliže porodice sa AB u velikoj meri povećava se rizik (34). Taj rizik se dodatno povećava ukoliko neko ima više od jednog člana najuže porodice obolelog od AB (38). Roditelj oboleo od AB povećava rizik bez obzira na nasleđivanje e4 alela, najverovatnije zbog negenetskih faktora poput istih uslova života i navika (39).

Modifikujući faktori rizika su faktori rizika koji se mogu menjati da bi se smanjio rizik od obolevanja od AD. Ukazano je da bi prilagođavanje ovih faktora moglo da spreči ili odloži 40% slučajeva demencije (40). Naravno smanjivanje rizika ne znači sigurno prevenciju demencije. Osobe koje upražnjavaju mere koje smanjuju rizik od demencije i dalje mogu da obole, ali je manje verovatno da će se to dogoditi i ukoliko se dogodi osobe će oboleti mnogo kasnije nego oni koji nisu ništa preduzeli. Takođe, razvijanje demencije ne mora da bude povezano sa lošim navikama koje direktno utiču na mozak. Mozak troši 20% kiseonika i energije. Zbog toga, faktori koji povećavaju rizik od kardiovaskularnih bolesti takođe povećavaju rizik od AD. Primeri takvih faktora rizika su: pušenje (41), dijabetes (42), gojaznost u srednjoj životnoj dobi (43,44), hipertenzija (45,46), prehipertenzija (47), i visok holesterol (48), za koje je dokazano da povećavaju rizik od AD. Ako se uzme u obzir kardiovaskularni aspekt prevencije demencije, dokazano je da fizička aktivnost (45,50) i pravilna ishrana (51,52) smanjuju rizik od AD u poređenju sa korišćenjem suplemenata, poput vitamina C, D i E,

the population. Additionally, it is expected that 68% of the global prevalence of dementia by 2050 will be in low and middle-income countries for which there is no evidence of decreasing risk of dementia (25).

Mortality

In the USA, Alzheimer's disease is a leading cause of death both amongst individuals age 65 and over (fifth place) and in the entire population (sixth place) (26). The most severe form of Alzheimer's disease frequently causes severe complications like immobility or pneumonia, and pneumonia is the most common immediate cause of death in people with Alzheimer's dementia (27). Like many other acute conditions, pneumonia is frequently listed as the primary cause of death for individuals with Alzheimer's (28), which results in difficulty determining the actual number of deaths from Alzheimer's. It was recently published in a study that only 5% of the total 14% of deaths in Americans aged 70 or older were properly attributed to dementia on the death certificate between 2000-2009 (29). However, it is even more complicated to properly attribute deaths to Alzheimer's as approximately 15% to 30% of individuals diagnosed with Alzheimer's dementia have dementia due to another cause (7,8).

In the last 20 years, Alzheimer's disease has increased by 145.2% as the recorded cause of death, representing both deaths being properly attributed to Alzheimer's disease more frequently and Alzheimer's more commonly being the cause of death due to the aging of the population (26). On average, individuals diagnosed with Alzheimer's dementia survive for four to eight years, living even up to 20 years in rare cases (30). Because of this, it is estimated that two-thirds of individuals deceased due to dementia die in nursing homes (31).

Based on years of life lost (YLL), Alzheimer's disease was the fourth, according to years of life with disability (YLD) nineteenth and according to the sum indicator DALY (Disability Adjusted Life Years - DALY) sixth leading cause of burden amongst diseases in the USA in 2016. (32)

Risk Factors

Late-onset Alzheimer's, which is the manifestation of Alzheimer's amongst individuals age 65 or older, is the most common form of Alzh-eimer's disease. It is believed to result from multiple rather than one factor. The nonmodifiable risk factors for Alzheimer's disease are age, genetics, and family history. These nonmodifiable factors are also the most important risk factors for late-onset Alzheimers. Age is the most significant factor as the percentages of people with Alzheimer's dementia greatly increase with age. In the USA, only 5.3 % of individuals in the age range 65-75 have Alzheimer's dementia; there is a significant increase to 13.8 % in the range of 75-84, and 34.6% of individuals over the age of 85 have this type of dementia(5). It is important to remember that Alzheimer's dementia is not a normal part of the aging process and that age alone is not a sufficient cause for developing Alzheimer's dementia (33).

Multiple genes that increase the risk of developing Alzheimer's have been found, the most notable being the APOE-e4 gene, as it has impacts late-onset Alzheimer's risk the most. This gene codes for one of the cholesterol transporting proteins in the bloodstream, and all people inherit one of three alleles of this gene from each parent. The alleles are e2, e3, and e4, so there are six possible allele combinations. Having the e4 form increases risk compared to the e3 form, and having the e2 form decreases risk compared with the e3 form. I.e., individuals with e4/e3 or e4/e2 have three times higher risk of developing Alzheimer's than people with the e3/e3 form, while individuals with e4/e4 form have an 8-12 times greater risk of developing Alzheimer's than people with e3/e3 form(34-36). This is most likely due to individuals with the e4 form having a higher chance of beta-amyloid accumulation earlier in their lives than people with the other two alleles(37).

A family history of Alzheimer's is not required to get the disease, but having a first-degree relative with Alzheimer's greatly increases the risk (34). That risk is further increased if an individual has more than one first-degree relative with Alzheimer's disease (38). A parent with Alzheimer's increases the risk regardless of e4 allele inheritance, most likely due to shared non-genetic factors like living conditions and life habits (39).

Modifiable risk factors are risk factors that can be changed to decrease the risk of developing Alzheimer's dementia. It has been suggested that adjusting these factors could prevent or delay 40% of dementia cases(40). Naturally, reducing

za koje je pokazano da nisu efikasni u smanjivanju obolevanja od ove bolesti (53).

Pokazano je da duže formalno obrazovanje smanjuje rizik od AB (54,55). Veruje se da je to zbog toga što mozak razvija sposobnost da na fleksibilan i efikasan način koristi neuralnu mrežu, koja omogućava da se kognitivni zadaci obavljaju uprkos promenama u mozgu (56,57). Takođe, rad u sredini koja je mentalno stimulativna, i bavljenje stimulativnim aktivnostima, ima sličan efekat (58). Razlog ovih odnosa je nepoznat, međutim, duže formalno obrazovanje je obično znak višeg socioekonomskog statusa, što je protektivni faktor (59). Još jedan primećen trend je da osobe kraćeg formalnog obrazovanja imaju više kardiovaskularnih rizika, koji su već dokazani kao rizici za AB.

Neke studije ukazuju da socijalne i mentalne aktivnosti imaju dobrobiti za zdravlje mozga i da smanjuju rizik za AB (60,61), međutim moguće je da je ova veza primećena zato što ljudi sa oštećenjem mozga i AB gube želju za socijalnim i mentalnim aktivnostima. Sve ovo ukazuje na neophodnost sprovođenja daljih istraživanja.

Traumatska povreda mozga (TPM) narušava normalnu funkciju mozga kao posledica povrede glave i pokazano je da povećava rizik od demencije (62). Najčešće je trauma izazvana saobraćajnim nesrećama i nakon udarca u neki predmet (63). Svaka TPM dalje povećava rizik od demencije (64); dokazano je da čak i blage TPM povećavaju rizik od demencije (64), dok osobe koje su imale TPM dobijaju AB ranije od osoba bez istorije takve povrede.

Hroničnu traumatsku encefalopatiju (HTE) izazivaju ponovljeni udarci u glavu, povrede koje se obično dobijaju u kontaktnim sportovima. Na primer, igrači američkog fudbala imaju 30% veći rizik da dobiju HTE po godini igranja (65). Jedan pregledni članak navodi ponovnu traumu mozga kao najveći faktor rizika za razvijanje promena na mozgu povezanih sa HTE (66). Zajednička stvar za HTE i AB su abnormalni čvorovi tau proteina u mozgu, dok su beta-amiloidni plakovi retki u THE (62,63).

Među ostalim faktorima rizika koji pokazuju potencijalno značajnu vezu sa AB su nedovoljan ili loš san (67), zloupotreba alkohola (68), depresija (69) i oštećenje sluha (70). Daunov sindrom, takođe, predstavlja značajan faktor rizika za AB s obzirom da su osobe sa ovim sindromom rođene sa tri kopije 21. hromozoma, koji kodira proizvodnju amiloidnog prekursorskog proteina i može da poveća beta-amiloidnu proizvodnju u mozgu. Stoga je to najverovatnije razlog zašto 30% osoba sa Daunovim sindromom uzrasta od 50 do 60 godina i 50% starijih od 60 godina imaju AB (71).

Biomarkeri

Biomarkeri su merljive biološke promene koje mogu da se koriste da se utvrdi da li neka osoba ima neku bolest ili je u riziku da oboli. U slučaju AB, ovi biomarkeri su nagomilavanje fragmenata beta-amiloidnog proteina što formira beta-amiloidni plak van neurona i nagomilavanje abnormalnog tau proteina unutar neurona. Beta-amiloidni plak i njegovi oligomeri utiču na komunikaciju između neurona u sinapsama, dok sa druge strane nagomilani abnormalni tau protein sprečava transport nutrijenata i drugih molekula koji su ključni za neurone i njihovu funkciju. Iako nema dovoljno podataka o sveobuhvatnim mehanizmima AB, povećano nagomilavanje beta-amiloida se povezuje sa daljim povećanjem količine tau proteina (72,73). Toksični efekti ova dva proteina aktiviraju imunske ćelije mozga, mikroglije, koje pokušavaju da očiste toksične proteine i mrtve ćelije. Ako je stopa odumiranja ćelija prebrza da bi ih mikroglije očistile, to može dovesti do hroničnog zapaljenja. Atrofija ili smanjena zapremina mozga se javlja zbog gubitka ćelija. Još jedan uobičajen simptom AB koji dalje negativno utiče na moždanu funkciju je smanjena sposobnost mozga da metaboliše njegov primarni izvor energije, glukozu. Veza između ovih biomarkera sa AB je potvrđena kroz studije na ljudima koji su dominantno imali naslednu AB. Ovi ljudi imaju retka genetska stanja koja izazivaju AB, i utvrđeno je da su kod njih nivoi beta-amiloidnih proteina u mozgu bili značajno povišeni 22 godine pre nego što se očekivalo da će se simptomi pojaviti (74). Takođe, metabolizam glukoze je kod njih počeo da opada 18 godina pre nego što su simptomi bili očekivani, dok je atrofija mozga počela da se javlja 13 godina pre očekivanog vremena za simptome (74). Druga studija na ovom tipu pacijenata je otkrila da količina abnormalnog tau proteina počinje da raste kada beta-amiloidni plakovi počnu da se formiraju, što može da bude dve decenije pre formiranja tau čvorova (75).

Veruje se da će upotreba pozitronske emisione tomografije mozga, kao i analiza proteinskog sastava likvora i krvi postati nezamenjivi alati za otkrivanje AB dovoljno rano za adekvatan farma-

risk factors does not mean assured dementia prevention. Individuals practicing measures that reduce the risk of dementia can still develop it, but it is significantly less likely to happen, and if it does happen, the individuals will develop it much later in their lives compared to those who had done nothing about it. Furthermore, developing dementia does not have to be linked to bad practices that directly impact the brain. The brain consumes 20% of oxygen and energy supply. Because of that, factors that increase the risk of developing cardiovascular disease also increase the risks of developing Alzheimer's dementia. Examples of such factors are smoking (41), diabetes (42), midlife obesity (43,44), hypertension (45,46), prehypertension(47), and high cholesterol (48), which have all been proven to increase the risk of Alzheimer's dementia. In relation to the cardiovascular aspect of dementia prevention, physical activity (45-50) and a healthy diet (51,52) both reduce risks of Alzheimer's dementia compared to supplements like vitamins C, D, and E, which have been shown as ineffective at reducing the chance of this illness (53).

It has been shown that a longer formal education lowers the risk for Alzheimer's (54,55). It is believed this is due to the brain developing the ability to make flexible, efficient use of the neural network, making performing cognitive tasks easier despite changes in the brain (56,57). In addition, being employed in a mentally stimulating environment and engaging in other mentally stimulating activities achieves a similar effect (58). The reason for these relations is unknown, however, longer formal education is usually a sign of a higher socioeconomic status, which is a protecting factor (59). Another observed trend is that individuals with shorter formal education have more cardiovascular risks, which have already been proven as Alzheimer's risks.

Some studies suggest that social and mental activity are beneficial for brain health and reduce Alzheimer's risk (60,61), but it could also be possible that this correlation is seen because people with brain damage and Alzheimer's lose the desire for social and mental activity. All these facts point towards the necessity of conducting further research.

Traumatic Brain Injury (TBI) disrupts normal brain function due to head injury and has been shown to increase the risk of dementia (62). Most frequently, the trauma is caused in car accidents and upon being impacted by an object (63). Each TBI further increases the risk of dementia (64); it has been proven that even mild TBI's double the risk of dementia (64), and individuals that had TBI get Alzheimer's at an earlier age than individuals with no history of that injury.

Chronic traumatic encephalopathy (CTE) is caused by repeated blows to the head, often sustained in contact sports. For example, football players have a 30% increased risk of developing CTE per year played (65). A review article identifies repetitive brain trauma as the biggest risk factor for developing CTE-related brain changes (66). The common thing about CTE and Alzheimer's is abnormal protein tau tangles in the brain, however, beta-amyloid plaques are rare in CTE (62,63).

Among the other risk factors studied that show a potential significant relation to Alzheimer's disease are insufficient or poor sleep (67), alcohol abuse(68), depression (69), and hearing impairment (70). Down syndrome is also a significant risk factor for Alzheimer's disease as individuals with it are born with three copies of the chromosome 21, which codes for APP production and may increase beta-amyloid production in the brain. That is the most likely reason why 30% of individuals with Down syndrome age 50-60 and 50% age 60 and older have Alzheimer's (71).

Biomarkers

Biomarkers are measurable biological changes that can be used to determine whether an individual has a disease or a risk of developing it. In Alzheimer's disease, these biomarkers are accumulation of the beta-amyloid protein fragment forming beta-amyloid plaques outside of neurons and accumulation of abnormal tau protein inside neurons. Beta-amyloid plaques and their oligomers interfere with the communication between neurons at synapses, while on the other hand, accumulated abnormal tau protein prevents the transport of nutrients and other molecules that are vital for the neurons and their function. Although there is much to be learned about the overarching mechanisms of Alzheimer's disease, increasing beta-amyloid accumulation is associated with subsequent increases in the amount of tau protein (72-73). These two proteins' toxic effects

kološki tretman koji potencijalno može zaustaviti ili usporiti progresiju bolesti kada odgovarajući lekovi postanu dostupni u budućnosti. Biomarkerski testovi će takođe biti ključni za praćenje efikasnosti lečenja i odabir pacijenata koji pate od specifičnih tipova Alchajmerove patologije za koju će lekovi biti dizajnirani (76). Najbolji test ili kombinacije testova će zavisiti od specifičnog stanja pacijenta (77).

Zaključak

AB je veliki javnozdravstveni problem zbog sve većeg broja obolelih naročito u populaciji starih 65 i više godina, koja je je u stalnoj ekspanziji. U bliskoj budućnosti najveći teret ove bolesti podneće zemlje u razvoju. Iz ovih razloga, posebnu pažnju treba posvetiti istraživanjima usmerenim na pronalaženje adekvatnog farmakološkog tretmana, kao i metoda za rano otkrivanje ovog oboljenja na osnovu biomarkera. Dok čekamo ovaj napredak u nauci, ne treba tapkati u mestu, već treba raditi na podizanju svesti o faktorima rizika za nastanak ovog oboljenja u cilju procene ličnog rizika i preduzimanja adekvatnih preventivnih mera.

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activate the brain immune cells, microglia, which attempt to clean the toxic proteins and dead cells. If the rate of decaying cells is too fast for the microglia to clean, it might lead to chronic inflammation. Atrophy or decreased brain volume occurs due to cell loss. Another common symptom of Alzheimer's disease that further negatively impacts brain function is the decreased ability of the brain to metabolize its primary energy source, glucose. The relationship of these biomarkers to Alzheimer's was confirmed through studies on people with dominantly inherited Alzheimer's disease. These people have rare genetic conditions that cause Alzheimer's, and it was determined that they had significantly increased beta-amyloid levels in the brain 22 years before symptoms were expected to develop (74). Additionally, glucose metabolism started deteriorating 18 years before the symptoms were expected, while brain atrophy started occurring 13 years before the expected time for symptoms (74). A different study on this patient type revealed that the amount of abnormal tau protein starts increasing when beta-amyloid plaques start forming, which can be up to two decades prior to the formation of tau tangles (75).

It is believed that the use of positron emission tomography to study the brain as well as analysis of cerebrospinal fluid and blood protein composition will become irreplaceable tools for identifying Alzheimer's disease early enough to receive proper pharmacological care with the potential to stop or slow the progression of Alzheimer's disease when these treatments become available in the future. The biomarker tests will also be critical for observing the efficiency of the treatment and selecting patients who suffer from specific types of Alzheimer's pathology the drugs will be designed to affect (76). The best tests or test combinations will warry depending on the patients' specific conditions (77).

Conclusion

Alzheimer's disease is a major public health issue due to the ever-growing number of diseased individuals, especially in the continuously expanding population of people age 65 and over. In the near future, developing countries will bear the largest burden of this disease. For these reasons, special attention must be given to research focused on finding appropriate pharmacological treatments and on early biomarker-based detection methods. While we wait for these scientific advancements, we must not stand idle but need to raise awareness about known risk factors for this illness to assess personal risk and take adequate preventive measures.

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