Poremećaji spavanja u Alzheimerovoj bolesti – od kliničke slike do neurobioloških nalaza

/ Sleep Disorders in Alzheimer's Disease: from Clinical Presentation to Neurobiological Findings

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Poremećaji spavanja su učestali rani simptom Alzheimerove bolesti (AB) i vodeći uzrok smanjene kvalitete života bolesnika s AB. S neurobiološke strane poremećaji spavanja su iznimno važni jer omogućuju uvid u rane mehanizme i neurodegenerativne procese specifične za AB. Mnoga istraživanja ukazuju da su poremećaji spavanja u AB uzrokovani selektivnom degeneracijom jezgara koje potiču budnost i spavanje, a koje se nalaze u moždanom deblu i hipotalamusu. Od posebne je važnosti poremećaj sporovalnog spavanja koji dovodi do porasta razine tau proteina i beta amiloida u mozgu, što vjerojatno ima važnu ulogu u patofiziologiji AB. Osmišljavanje prospektivnih istraživanja koja kombiniraju opsežne kliničke podatke s modernim neuropatološkim metodama obećavajući su pristup za bolje razumijevanje biološke podloge poremećaja spavanja i razvoja terapije učinkovite u ranim stadijima AB.

***/** Sleep disorders are common early symptoms of Alzheimer's disease (AD) and the leading cause of quality of life impairment in AD patients. In terms of neurobiology, sleep disorders are of exceptional importance as they may provide insight into early mechanisms and neurodegenerative processes specific to AD. Growing data indicate that sleep disruption in AD is caused by selective degeneration of sleep- and wake-promoting nuclei in the brain stem and hypothalamus. Disruption of slow-wave sleep increases the concentration of tau and amyloid-beta in the brain, which may represent an important part of the pathophysiology of AD. Designing prospective studies that combine comprehensive clinical data with modern neuropathological analyses is a promising strategy to elucidate the biological basis of sleep disorders, and open new avenues for early treatments of AD.*

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Alzheimerova bolest (AB) se često manifestira neuropsihijatrijskim (NPS) ili nekognitivnim simptomima. Premda su ti simptomi opisani već u prvim izvješćima o AB i bili sastavni dio koncepta ove bolesti (1), istraživanja su tradicionalno bila usmjerena na kognitivne simptome, posebice poremećajima pamćenja, kao i odgovarajućoj patologiji medijalnog sljepoočnog režnja mozga. U posljednjem desetljeću poraslo je zanimanje za razumijevanjem NPS specifičnih za Alzheimerovu bolest, posebice za poremećaje spavanja. Poremećaji spavanja su vodeći uzrok smanjene kvalitete života bolesnika i predstavljaju najveće opterećenje za njegovatelje i obitelj bolesnika (2, 3). Farmakološko liječenje poremećaja spavanja nije vrlo učinkovito i ograničeno je značajnim neželjenim popratnim učincima, poput porasta mortaliteta bolesnika s AB (4, 5). Nefarmakološko liječenje poput bihevioralno-terapijskih pristupa ili unaprjeđenja kvalitete rasvjete pokazuju obećavajuće rezultate, ali ih je teško primijeniti u praksi (6, 7). Da bismo unaprijedili liječenje potrebno je bolje razumijevanje neurobiološke podloge NPS u AB. U tom smjeru sve je vise radova koji pokazuju da se prve patološke promjene u AB javljaju u subkortikalnim regijama mozga, tocnije u moždanom deblu. Nadalje, čini se da patologija moždanog debla predstavlja biološki korelat ranih NPS u AB (8-10). Podatci istraživanja na staničnim kulturama, životinjskim modelima bolesti, kao i rezultati kliničkih istraživanja ukazuju da poremećaji spavanja, posebice poremećaji NREM sporovalnog spavanja igraju važnu ulogu u AD (11). Čini se da su poremećaji spavanja ne samo posljedica neurodegenerativnih promjena, nego i rizični čimbenik ili jedan od uzročnih čimbenika uključenih u patofiziologiju AB. Cilj ovog preglednog rada je sažeto iznijeti kliničku sliku i neurobiološku podlogu poremećaja spavanja u AB. Posebno ću se osvrnuti na rezultate istraživanja postmortalnih uzoraka čovječjeg mozga (moždanog debla i hipotalamusa) te poremećaja NREM spavanja. Poremećaji cirkadijalnog

Neuropsychiatric symptoms (NPS) or non-cognitive symptoms are common manifestations of Alzheimer's disease (AD). Although these symptoms were included in the first reports and early conceptualization of dementia (1), research efforts have traditionally been focused on the cognitive symptoms of AD, such as memory impairment, and the corresponding pathology in the medial temporal lobe. In the last decade, however, there has been a growing interest in understanding AD-specific NPS, particularly sleep disorders. Sleep disorders are leading causes of quality of life impairment in AD patients and place major burdens on these patients' caregivers and families (2,3). To date, the pharmacological treatments available to treat sleep disorders have limited efficacy and carry great risk of serious side effects, including mortality (4, 5), while non-pharmacological, behaviour-cantered treatment options, as well as improvement of light conditions, show promising but limited results and prove difficult to implement (6,7). A better understanding of the neurobiological basis of AD NPS is needed to develop new treatment strategies. There is growing evidence that the first pathological changes in AD arise in the brain's subcortical structures, namely the brain stem. The brain stem also appears to be a neurobiological correlate of early AD NPS (8-10). Furthermore, converging data from experiments involving cell cultures, animal models, and clinical studies show that sleep disorders, especially those affecting non-REM sleep (NREM), play an important, bidirectional role in AD (11). In other words, sleep disorders are not only a secondary consequence of neurodegeneration, but they are likely risk factors for, or even cause, the pathophysiological processes in AD. The goal of this article is to concisely review the clinical presentations and neurobiological basis of sleep disorders in AD. To accomplish this goal, emphasis will be given to experiments that imaged post-mortem brain tissue (specifically from the brainstem and hypothalamic regions) of humans who experienced NREM sleep disturbances. Although of

ritma nisu tema ovog rada, ali će s obzirom na povezanost spavanja i cirkadijalnog ritma biti prigodno spomenuti.

PROMJENE SPAVANJA TIJEKOM STARENJA I ALZHEIMEROVE BOLESTI

Mnoga istraživanja su pokazala da se trajanje i kvaliteta spavanja mijenjaju tijekom normalnog starenja. Na primjer, tijekom života se skraćuje ukupno trajanje spavanja, dok fragmentacija sna, pospanost i broj drijemanja (ili kratkog sna) tijekom dana rastu (12-14). Nadalje, EEG-snimanja pokazuju da se sporovalno, ali i REM spavanje, kao i vretena spavanja sa starenjem skraćuju (15, 16).Zanimljivo je da bolesnici s AB imaju sličan obrazac promjene spavanja, koje su međutim u usporedbi s normalnim starenjem učestalije i izraženije. Podatci epidemioloških istraživanja povezuju poremećaje spavanja s kognitivnim poremećajima i povećanim rizikom za razvoj demencije (17-19). Tako su Moran i sur. pokazali da gotovo četvrtina bolesnika s AB imaju poremećaje spavanja (20). Nadalje, poremećaji spavanja pozitivno koreliraju s trajanjem AB i narušavanjem kvalitete života (21). Tipični poremećaji spavanja koji se javljaju u AB su: produljeno trajanje spavanja, pospanost tijekom dana, učestalije drijemanje tijekom dana, kraće vrijeme usnivanja (latencija sna) tijekom dana, ali dulje vrijeme usnivanja tijekom noći, fragmentacija sna i uranjeno jutarnje buđenje (21-24). U uznapredovalim stadijima AB vrijeme spavanja tijekom dana i noći može čak biti jednakog trajanja. Taj nalaz, kao i sindrom zalazećeg sunca (smetenost i simptomi delirija u večernjim satima) ukazuju na poremećaj cirkadijalnog ritma u bolesnika s AB. Klinički podatci potkrijepljeni su nalazima EEG-a, koji pokazuju poremećaj NREM ili sporovalnog spavanja, kao i smanjenu učestalost vretena spavanja i K-kompleksa u bolesnika s AB (25, 26). Nadalje, poznato je su

key importance for the regulation of the sleep and wake cycling, circadian rhythm sleep disorders will not be the focus of this review, but they will be mentioned when pertinent.

SLEEP CHANGES DURING AGING AND ALZHEIMER'S DISEASE

There is strong evidence that the duration and quality of sleep changes throughout normal aging. For example, over the course of the lifespan, total sleep duration decreases while sleep fragmentation, daytime sleepiness, and number of naps taken per day increases (12-14). Additionally, EEG-recordings show age-related reductions in slow-wave sleep (SWS) and REM sleep, as well as sleep spindle activity (15,16). Interestingly, research on AD patients shows similar, but more frequent and more extensive sleep disruption. Epidemiological data links sleep disorders with cognitive impairment and a heightened risk for dementia (17-19). A study conducted by Moran and colleagues found that 24.5% of AD patients reported sleep disturbances (20). Furthermore, sleep disorders correlate with the duration of AD and impairment of activities of daily living (21). Typical sleep disorders in AD are: sleeping more than usual and sleepiness during the day, increased daytime napping, shorter time to fall asleep (sleep latency) during the day, but longer sleep latency during the night, sleep fragmentation, early morning wakening (21-24). In advanced AD, the sleep time during the night and day can even equal. This finding together with the phenomenon of sundowning in patients with AD is highly indicative for circadian sleep disorders. Clinical data are supported by EEG studies particularly showing impairment of NREM sleep or slow-wave sleep (SWS), as well as reduced sleep spindles and K complexes in patients with AD (25,26). The findings that clinically and electrophysiologically documented sleep disorders are associated with impaired cognition (25,26) and that NREM-sleep plays a ma-

poremećaji spavanja, ustanovljeni na temelju kliničkih i elektrofizioloških pretraga, povezani s kognitivnim poremećajima (25, 26), kao i da NREM-spavanje ima važnu ulogu u konsolidaciji pamćenja (27). Navedeno jasno ukazuje na povezanost između spavanja i demencije.

SPAVANJE UTJEČE NA RAZINU TAU-PROTEINA I BETA-AMILOIDA U MOZGU

Razumijevanje međusobnog utjecaja spavanja i demencije značajno je unaprijeđeno radom Kanga i suradnika (2009). Oni su istraživanjem na mišjem modelu AB pokazali fiziološke fluktuacije razine beta-amiloida u mozgu: razina beta-amiloida opada poslije spavanja, a raste kao posljedica deprivacije sna (28). Upotrebom nove metode mjerenja stope proizvodnje i raščišćavanja (klirensa) proteina u cerebrospinalnom likvoru čovjeka, dokazan je sličan cirkadijalni obrazac razine tau-proteina i beta-amiloida kod zdravih ispitanika (29). Nadalje, pokazalo se da je cirkadijalna promjena razine tih proteina poremećena nakon stvaranja amiloidnih plakova (30). Poremećaji aktivnosti sporovalnog spavanja već nakon nekoliko dana povećavaju razinu tau-proteina u likvoru (31), što je povezano s većim opterećenjem tau-proteinima u mozgu mjerenim tau-PET-om (32). Navedeni nalazi potkrjepljuju epidemiološke podatke da kognitivno asimptomatski pojedinci s patološkom razinom beta-amiloida u mozgu ili likvoru slabije spavaju tijekom noći i imaju veću potrebu za spavanjem tijekom dana (19).

NEURONSKE MREŽE KOJE POTIČU BUDNOST I NREM SPAVANJE

Sustav regulacije spavanja i budnosti je složen, uključuje brojne neurotransmitorske sustave koji utječu jedni na druge, a potječu iz možda-

jor role in memory consolidation (27) represent an important link between sleep and dementia.

SLEEP INFLUENCES BRAIN LEVELS OF TAU AND AMYLOID-BETA

Our understanding of the association between sleep and dementia has been expanded through the seminal work of Kang et al. (2009), who used AD mutant mice to show a physiological diurnal fluctuation of amyloid-beta (Aβ): Aβ levels decrease in the brain after sleep and increase during sleep deprivation (28). A new method used to quantify protein production and clearance rate in cerebrospinal fluid (CSF) reported similar rapid Aβ turnover in healthy human participants (29). Recent research on human subjects showed that circadian fluctuation of Aβ and tau in CSF is disrupted after brain plaque formation (30). Furthermore, disruption of NREM slow-wave activity increases CSF tau levels over several days (31) and is associated with higher cortical tau-burden as measured by tau-PET (32). These findings corroborate the epidemiological data reporting that cognitively asymptomatic individuals with amyloid deposition, as assessed by Aβ42 levels in CSF, have decreased sleep efficiency and more frequent napping compared to those without amyloid deposition (19)

NETWORKS PROMOTING WAKEFULNESS AND NON-REM SLEEP

The neural system regulating sleep and wake states is complex and involves mutually interacting neurotransmitter systems arising from the brain stem and hypothalamus. In 2001 Saper and colleagues formulated a widely accepted concept of switching activity in sleep- and wake-promoting networks (33). According to

nog debla i hipotalamusa. Saperi sur.su 2001. objasnili promjene iz stanja budnosti u spavanje i obrnuto sistemom sklopke (33). Prema toj hipotezi, međudjelovanje između centara u mozgu koji potiču spavanje i onih koji potiču budnost ubrzava prijelaz između navedenih stanja. Na primjer, neuroni koji potiču spavanje, svojom aktivnošću istovremeno inhibiraju aktivnost neurona koji potiču budnost. Utišavanje sustava budnosti pridonosi dezinhibiciji neurona koji potiču spavanje čime se postiže brz i stabilan prijelaz u stanje spavanja.

Glavne jezgre koje potiču budnost nalaze se u moždanom deblu, hipotalamusu i bazi velikog mozga. U moždanom deblu budnost potiču noradrenergički neuroni u lokusu ceruleusu (LC) (34, 35), dopaminergički neuroni u ventralnoj tegmentalnoj areji (VTA) (36, 37) i serotonergički neuroni u dorzalnim jezgrama raphe (DRN) (38, 39). Navedene jezgre imaju opsežne projekcije u moždanu koru, talamus, hipotalamus i bazu mozga. U ponsu, glavne jezgre za budnost su glutamatergička parabrahijalna jezgra (PB) i preceruleus (PC) (40, 41). Kolinergičke jezgre aktivne tijekom budnosti uključuju pedunkulopontine (PPT) i laterodorzalne tegmentalne jezgre (LDT) (40, 41). Oreksinergički neuroni, smješteni u stražnjem dijelu lateralne areje hipotalamusa (LHA) su od posebne važnosti za stanje budnosti. Ti se neuroni projiciraju u moždano deblo, hipotalamus i LC (42). U blizini LHA nalazi se tuberomamilarna jezgra (TMN), koja obiluje histaminergičkim neuronima (43). Ostale kolinergičke, ali i GABAergičke i glutamatergičke skupine neurona aktivne tijekom budnosti nalaze se u bazi mozga (44).

Jezgre talamusa same po sebi ne potiču stanje budnosti, nego sudjeluju kao relejne jezgre primajući projekcije iz gore navedenih dijelova moždanog debla i hipotalamusa. Jezgre talamusa opsežno opskrbljuju moždanu koru glutamatergičkom inervacijom (45).

Najbitniji dijelovi sustava koji promiče spavanje su neuroni koji sadrže galanin i GABA-u, a

the sleep switch hypothesis, there is a reciprocal interaction between sleep- and wake-promoting brain regions. For example, when sleep-promoting neurons fire rapidly during sleep, they simultaneously inhibit the wake-promoting neurons. The silencing of the arousal system also contributes to the disinhibition of the sleep nuclei, which ensures a relatively rapid and stable switch into the sleep state.

The main wake-promoting nuclei are located in the brain stem, hypothalamus, and basal forebrain. The wake-promoting nuclei in the brain stem include the noradrenergic neurons of the locus coeruleus (LC) (34,35), the dopaminergic neurons of the ventral tegmental area (VTA) (36,37), and the serotoninergic dorsal raphe nuclei (DRN) (38,39). These nuclei project abundantly to the cerebral cortex, thalamus, hypothalamus and basal forebrain. The pontine glutamatergic parabrachial nucleus (PB) and precoeruleus (PC) area are two other wake-promoting nuclei in the brain stem (40,41). The cholinergic brain stem nuclei, which are also active during wakefulness, include the pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT) (40,41). The orexinergic neurons, located in the posterior part of the lateral hypothalamic area (LHA), are of particular importance during wakefulness. These neurons project to the brain stem, hypothalamus and LC (42). Anatomically close to the LHA is the tuberomammillary nucleus (TMN), which is abundant with histaminergic neurons (43). Other cholinergic, but also GABAergic and glutamatergic neuronal groups active during wakefulness can be found in the basal forebrain (44).

Although the thalamic nuclei do not have an intrinsic wake-promoting function, they are involved in wakefulness as relay nuclei that receive innervation from brain stem and hypothalamic structures and, in turn, provide extensive glutamatergic innervation of the cerebral cortex (45).

Major parts of the NREM sleep-promoting networks are neurons containing galanin and

koji se nalaze u intermedijanoj (ImN) ili ventrolateralnoj preoptičkoj jezgri (VLPO) hipotalamusa (46-48). Ti se neuroni projiciraju u TMN, LC, DNR, periakveduktalnu sivu tvar (PAG), PB i LHA. Druga bitna regija preoptičkog hipotalamusa je medijana preoptička jezgra (MnPO), koja sadrži GABAergičke neurone (49, 50). MnPO opsežno inervira VLPO, LHA, LC, DRN i PAG. Nedavna istraživanja provedena na glodavcima pokazala su da GABAergički neuroni parafacijalne zone (PZ) u produljenoj moždini potiču sporovalnu moždanu aktivnost. Oni se projiciraju u PB jezgru koja posljedično šalje glutamatergičku inervaciju u bazu mozga (51).

NEUROPATOLOŠKI NALAZI U MONOAMINERGIČKIM JEZGRAMA MOŽDANOG DEBLA

Degeneracija noradrenergičkog lokusa ceruleusa u AD je dobro poznata (52-54). Opsežnom postmortalnom analizom 2322 čovječja mozga, Braak i suradnici su 2011. pokazali da se prve patološke promjene tau-proteina u mozgu vide u jezgrama moždanog debla, najčešće u LC (55). Sto se tiče zahvaćanja moždane kore, prvi patološki proces očekivano je vidljiv u transentorinalnom korteksu. Zanimljivo je da je bez iznimke svaki mozak s patološkim nalazom u transentorinalnom korteksu imao zahvaćeni LC. Detaljno istraživanje LC pokazuje da je 8 % neurona tau-pozitivno već u Braakovom stadiju 0 (56). S napredovanjem bolesti, volumen LC-a se smanjuje, ali broj tau-pozitivnih neurona ostaje stabilan (56, 57). Prvo sustavno istraživanje serotonergičkih rafe jezgara (DRN) u AB pokazalo je iznimnu količinu neurofibrilarnih snopovai 75 % smanjenje broja neurona (58, 59). DRN je najosjetljivija serotonergička jezgra u AB (60), koja je zahvaćena u ranom stadiju bolesti, čak i prije nego je transentorinalni korteks zahvaćen (56,60,61).

GABA, localized in the intermediate nucleus (ImN) or ventrolateral preoptic nucleus (VLPO) of the hypothalamus (46-48). These neurons project to TMN, LC, raphe nuclei, periaqueductal gray (PAG), PB, and LHA. Another hypothalamic region in the preoptic area is the median preoptic nucleus (MnPO), which contains GABAergic neurons (49,50). The MnPO projects vastly to VLPO, LHA, LC, DRN, and PAG. Recent work done in rodents shows that the GABAergic neurons of the medullary parafacial zone (PZ) promote slow-wave activity projecting to the PB nucleus which, in turn, provides glutamatergic innervation of the basal forebrain (51).

NEUROPATHOLOGICAL FINDINGS IN THE MONOAMINERGIC BRAINSTEM NUCLEI

Degeneration of the noradrenergic locus coeruleus in AD is well documented (52-54). In a comprehensive post-mortem brain analysis of 2322 subjects, Braak et al. 2011 report that the first pretangle tau pathology in the brain is seen in brain stem nuclei, most often the LC (55). In the cortex, the region affected in this pretangle stage is the transentorhinal cortex. Interestingly, transentorhinal cortex tau-pathology is always accompanied by brain stem involvement, providing strong evidence that the LC is the first brain region affected by tau pathology. A detailed examination of the LC demonstrates that around 8% of LC neurons are already tau-positive in Braak stage 0 (56). As the disease progresses, there is a reduction of LC volume, but the number of tau-positive LC neurons remains stable (56,57). The first systematic analysis of serotonergic dorsal raphe nuclei (DRN) in AD shows extraordinary burden of neurofibrillary tangles and around a 75% reduction of neurons (58,59). Further studies demonstrate that the DRN is the most vulnerable serotonergic nucleus in AD (60) and is affected in the early course of AD, even before the transentorhinal cortex (56,60,61).

NEUROPATOLOŠKI NALAZI U HIPOTALAMUSU

U hipotalamusu je, kao i u moždanom deblu, opisana opsežna ali selektivna degeneracija jezgara. Dok tijekom starenja dolazi do diskretnog smanjenja volumena i broja neurona u suprahijazmatičkoj jezgri (SCN), te su promjene u AB veoma opsežne (62).Golgijevom metodom obilježavanja neurona te elektronskom mikroskopijom SCN-a, supraoptičke jezgre (SON) i periventrikularne jezgre (PVN) otkriveno je značajno smanjenje broja neurona i dendritičkih ogranaka u postmortalnom tkivu bolesnika s Braakovim stadijem II/III Alzheimerove bolesti u odnosu na kontrolne uzorke (63). Čini se da je SCN značajnije pogođena od SON i PVN. S obzirom da SCN predstavlja središnji cirkadijalni sat organizma, ovaj nalaz predstavlja neuropatološki korelat ranog poremećaja ciklusa spavanja i budnosti u AB. Drugo istraživanje u kojem su korištene gore navedene metode pokazalo je smanjenje broja neurona i dendrita, kao i propadanje sinapsi u mamilarnim jezgrama bolesnika s ranim stadijem AB. Zanimljivo je da je pritom opisana mala količina neurofibrilarne patologije. Histaminergičke tuberomamilarne jezgre su opsežno istražene u AB. U ranim stadijima bolesti postoji značajan gubitak neurona i dendrita, kao i propadanja sinapsi tog područja. U kasnijim stadijima povećava se količina patoloških tau-proteina te se dodatno smanjuje broj neurona (64-66). Oh i sur. nedavno su pokazali izraženo propadanje oreksinergičkih i histaminergičkih neurona u AB, uključenih u održavanje budnosti. Broj neurona u LHA bio je manji za 75 %, dok je broj neurona u TMN bio manji za 60 %. Osim toga, dokazali su značajnu opterećenost navedenih regija neurofibrilarnom patologijom, kao i smanjenje broja neurona koji proizvode navedene neurotransmitore. Manje su poznate moguće promjene hipotalamičkih jezgara aktivnih tijekom spavanja. Postoje oprečni i neujednačeni nalazi

NEUROPATHOLOGICAL FINDINGS IN THE HYPOTHALAMUS

As in the brain stem, a profound but selective degeneration of hypothalamic nuclei has been reported. Research shows decreased volume and total cell counts in the suprachiasmatic nucleus (SCN) in senescence, and a dramatic reduction in AD (62). A Golgi and electron microscope study of SCN, supraoptic (SON), and paraventricular nucleus (PVN) reveals a substantial decrease in the neuronal population and a loss of dendritic branches in subjects with AD Braak stage II/III compared to controls (63). The SCN appears to be more severely affected than SON and PVN. Since the SCN constitutes the primary circadian clock in human, this finding likely represents a pathological correlate of early disruption of the sleep-wake cycle in AD. Another study using a Golgi and electron microscope demonstrated a significant loss of neurons and dendrites, as well as synaptic alterations in the mammillary bodies of patients with early stages of AD. Interestingly, minimal neurofibrillary pathology was reported. The histaminergic tuberomammillary area has been extensively studied in AD. In early AD stages, there is a significant loss of neurons and dendrites, as well as alterations to synapses in this area. Later AD stages exhibit tau-burden and a reduction of neurons (64-66). A study conducted by Oh and colleagues (2019) demonstrates extensive degeneration of orexinergic and histaminergic wake promoting nuclei in AD, with a 75% reduction of neurons in LHA containing orexin neurons, and a 60% neuronal loss in TMN. Significant tau-pathology and a reduction in the number of neurotransmitter-producing neurons is also detected. Less is known regarding sleep-promoting regions of the hypothalamus. Alterations in galanin-cell morphology and axonal varicosities is also reported with conflicting or inconsistent data regarding the number of galanin-cells in in SON, PV, and TM (67). A

što se tiče morfologije galaninergičkih neurona kao i njihovih aksona u SON, PV I TMN (67). Jedno istraživanje upućuje da je gubitak galaninergičkih neurona u ImN neuropatološki korelat fragmentacije sna u bolesnika s AB (68).

ZAKLJUČCI I SMJER BUDUĆIH ISTRAŽIVANJA

U posljednjem desetljeću svjedočimo iznimnom porastu znanja i razvoju novih znanstvenih metoda u temeljnim i kliničkim istraživanjima poremećaja spavanja u kontekstu neurodegenerativnih bolesti. Pokusi na mišjim modelima AB i novi eksperimentalni pristupi doveli su do uzbudljivih otkrića uloge spavanja u metabolizmu tau proteina u beta amiloida. To nam je omogućilo bolje razumijevanje patofiziologije spavanja u AB. Međutim, rezultate temeljnih, kliničkih i neuropatoloških istraživanja nije lako integrirati. Neuralni mehanizmi budnosti i spavanja su vrlo složeni, a većina podataka o fiziologiji sna i njegovim poremećajima potječe od istraživanja na životinjskim modelima. Čini se da je obećavajući pristup istraživanja tog područja unaprjeđenje metoda slikovnih prikaza mozga, kao i osmišljavanje prospektivnih studija koje kombiniraju opsežne kliničke podatke s modernim neuropatološkim metodama. Nove spoznaje o poremećajima jezgara koje potiču spavanja i budnost, kao i njihovih neurotransmitorskih sustava omogućit ce otkrivanje novih terapijskih ciljeva i osmišljavanje učinkovitih lijekova. U sirem smislu, ono sto smo naučili je da temeljite kliničko-patološke korelacije, uključujući opsežni neuropatološki nalaz mijenjaju smjer istraživanja u AB. Ako prve promjene u AB počinju u moždanom deblu, na što ukazuju trenutna istraživanja, onda je to regija koja bi trebala biti cilj istraživanja u potrazi za ranim patofiziološkim promjenama i ranim terapijskim intervencijama u AB.

recent study by Lim and colleagues (2014) correlates clinical sleep data with post-mortem finding and demonstrates that the loss of galaninergic neurons of the ImN is associated with sleep fragmentation (68).

CONCLUSIONS AND FUTURE DIRECTIONS

With growing knowledge and developments in basic and clinical sleep, research in the context of neurodegenerative disorders is proliferating like never before. Experiments using AD mouse models and novel experimental approaches in basic research have provided exciting new knowledge about the role of sleep in tau and amyloid metabolism and have given us a better understanding of the pathophysiology of sleep in AD. However, it is not easy to bring together experimental data from basic, clinical and neuropathological research. The neural mechanisms of arousal and sleep are extremely complex, with the majority of data on sleep physiology, and its disruption in AD comes from animal research. It seems that the improvement of imaging methods and the designing prospective studies, which can combine comprehensive clinical data with modern neuropathological analyses, are promising strategies that can be used to overcome this gap. Gaining more knowledge on the disruption of specific sleep- and wake-promoting nuclei and their neurotransmitter systems will provide us with targets for more effective drug development. Broadly speaking, what we have learned is that thorough clinico-pathological correlation, including comprehensive neuropathological examination, is changing the direction of Alzheimer research. If the first AD pathological changes arise in the brain stem, as current data suggest, then this is the region that should be investigated when researching early pathophysiological processes and therapeutic intervention in AD.

LITERATURA/*REFERENCES*:

1. Alzheimer A. Über einen eigenartigen schweren Erkrankungsprozeß der Hirnrinde. Neurologisches Centralblatt 1906;23:1129-36.
2. Spira AP, Chen-Edinboro LP, Wu MN, Yaffe K. Impact of sleep on the risk of cognitive decline and dementia. Curr Opin Psychiatry. 2014;27(6):478-83.
3. Spira AP, Kaufmann CN, Kasper JD, Ohayon MM, Rebok GW, Skidmore E, et al. Association between insomnia symptoms and functional status in U.S. older adults. J Gerontol B Psychol Sci Soc Sci. 2014;69 Suppl 1:S35-41.
4. Dauphinot V, Faure R, Omrani S, Goutelle S, Bourguignon L, Krolak-Salmon P, et al. Exposure to anticholinergic and sedative drugs, risk of falls, and mortality: an elderly inpatient, multicenter cohort. J Clin Psychopharmacol. 2014;34(5):565-70.
5. Weich S, Pearce HL, Croft P, Singh S, Crome I, Bashford J, *et al*. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. Bmj. 2014;348:g1996.
6. Figueiro MG, Lesniak NZ, Rea MS. Implications of controlled short-wavelength light exposure for sleep in older adults. BMC Res Notes. 2011;4:334.
7. Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. JAMA. 2008;299(22):2642-55.
8. Ehrenberg AJ, Suemoto CK, Franca Resende EP, Petersen C, Leite REP, Rodriguez RD, et al. Neuropathologic Correlates of Psychiatric Symptoms in Alzheimer's Disease. J Alzheimers Dis. 2018;66(1):115-26.
9. Grinberg LT, Rueb U, Heinsen H. Brainstem: neglected locus in neurodegenerative diseases. Front Neurol. 2011;2:42.
10. Simic G, Stanic G, Mladinov M, Jovanov-Milosevic N, Kostovic I, Hof PR. Does Alzheimer's disease begin in the brainstem? Neuropathol Appl Neurobiol. 2009;35(6):532-54.
11. Lucey BP, Holtzman DM. How amyloid, sleep and memory connect. Nat Neurosci. 2015;18(7):933-4.
12. Conte F, Arzilli C, Errico BM, Giganti F, Iovino D, Ficca G. Sleep measures expressing 'functional uncertainty' in elderlies' sleep. Gerontology. 2014;60(5):448-57.
13. Klerman EB, Dijk DJ. Age-related reduction in the maximal capacity for sleep--implications for insomnia. Curr Biol. 2008;18(15):1118-23.
14. Porter VR, Buxton WG, Avidan AY. Sleep, Cognition and Dementia. Curr Psychiatry Rep. 2015;17(12):97.
15. Landolt HP, Dijk DJ, Achermann P, Borbely AA. Effect of age on the sleep EEG: slow-wave activity and spindle frequency activity in young and middle-aged men. Brain Res. 1996;738(2):205-12.
16. Lombardo P, Formicola G, Gori S, Gneri C, Massetani R, Murri L, *et al*. Slow wave sleep (SWS) distribution across night sleep episode in the elderly. Aging (Milano). 1998;10(6):445-8.
17. Leng Y, Redline S, Stone KL, Ancoli-Israel S, Yaffe K. Objective napping, cognitive decline, and risk of cognitive impairment in older men. Alzheimers Dement. 2019;15(8):1039-47.
18. Spira AP, Stone KL, Redline S, Ensrud KE, Ancoli-Israel S, Cauley JA, *et al*. Actigraphic Sleep Duration and Fragmentation in Older Women: Associations With Performance Across Cognitive Domains. Sleep. 2017;40(8).
19. Ju YE, McLeland JS, Toedebusch CD, Xiong C, Fagan AM, Duntley SP, *et al*. Sleep quality and preclinical Alzheimer disease. JAMA Neurol. 2013;70(5):587-93.
20. Moran M, Lynch CA, Walsh C, Coen R, Coakley D, Lawlor BA. Sleep disturbance in mild to moderate Alzheimer's disease. Sleep Med. 2005;6(4):347-52.
21. Tractenberg RE, Singer CM, Kaye JA. Characterizing sleep problems in persons with Alzheimer's disease and normal elderly. J Sleep Res. 2006;15(1):97-103.
22. Shin HY, Han HJ, Shin DJ, Park HM, Lee YB, Park KH. Sleep problems associated with behavioral and psychological symptoms as well as cognitive functions in Alzheimer's disease. J Clin Neurol. 2014;10(3):203-9.
23. Carpenter BD, Strauss M, Patterson MB. Sleep Disturbances in Community-Dwelling Patients with Alzheimer's Disease. Clinical Gerontologist. 1996;16(2):35-49.
24. McCurry SM, Logsdon RG, Teri L, Gibbons LE, Kukull WA, Bowen JD, *et al*. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. J Geriatr Psychiatry Neurol. 1999;12(2):53-9.
25. Tworoger SS, Lee S, Schernhammer ES, Grodstein F. The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women. Alzheimer Dis Assoc Disord. 2006;20(1):41-8.
26. Moe KE, Vitiello MV, Larsen LH, Prinz PN. Symposium: Cognitive processes and sleep disturbances: Sleep/wake patterns in Alzheimer's disease: relationships with cognition and function. J Sleep Res. 1995;4(1):15-20.
27. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11(2):114-26.
28. Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, *et al*. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science. 2009;326(5955):1005-7.
29. Bateman RJ, Munsell LY, Morris JC, Swarm R, Yarasheski KE, Holtzman DM. Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. Nat Med. 2006;12(7):856-61.
30. Roh JH, Huang Y, Bero AW, Kasten T, Stewart FR, Bateman RJ, *et al*. Disruption of the sleep-wake cycle and diurnal fluctuation of beta-amyloid in mice with Alzheimer's disease pathology. Sci Transl Med. 2012;4(150):150ra22.
31. Ju YE, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology--a bidirectional relationship. Nat Rev Neurol. 2014;10(2):115-9.

32. Lucey BP, McCullough A, Landsness EC, Toedebusch CD, McLeland JS, Zaza AM, et al. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. Sci Transl Med. 2019;11(474).
33. Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci. 2001;24(12):726-31.
34. Harley CW. A role for norepinephrine in arousal, emotion and learning?: limbic modulation by norepinephrine and the Kety hypothesis. Prog Neuropsychopharmacol Biol Psychiatry. 1987;11(4):419-58.
35. Szabadi E. Functional neuroanatomy of the central noradrenergic system. J Psychopharmacol. 2013;27(8):659-93.
36. Dahlstroem A, Fuxe K. Evidence for the existence of monoamine-containing neurons in the central nervous system I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol Scand Suppl. 1964:Suppl 232:1-55.
37. Dahlstrom A, Fuxe K. Localization of monoamines in the lower brain stem. Experientia. 1964;20(7):398-9.
38. Baker KG, Halliday GM, Tork I. Cytoarchitecture of the human dorsal raphe nucleus. J Comp Neurol. 1990;301(2):147-61.
39. Baker KG, Halliday GM, Halasz P, Hornung JP, Geffen LB, Cotton RG, *et al*. Cytoarchitecture of serotonin-synthesizing neurons in the pontine tegmentum of the human brain. Synapse. 1991;7(4):301-20.
40. Steriade M, Datta S, Pare D, Oakson G, Curro Dossi RC. Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. J Neurosci. 1990;10(8):2541-59.
41. el Mansari M, Sakai K, Jouvet M. Unitary characteristics of presumptive cholinergic tegmental neurons during the sleep-waking cycle in freely moving cats. Exp Brain Res. 1989;76(3):519-29.
42. Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, *et al*. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci. 1998;18(23):9996-10015.
43. Panula P, Airaksinen MS, Pirvola U, Kotilainen E. A histamine-containing neuronal system in human brain. Neuroscience. 1990;34(1):127-32.
44. Jones BE. Activity, modulation and role of basal forebrain cholinergic neurons innervating the cerebral cortex. Prog Brain Res. 2004;145:157-69.
45. Jones EG, Leavitt RY. Retrograde axonal transport and the demonstration of non-specific projections to the cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey. J Comp Neurol. 1974;154(4):349-77.
46. Bonnefond C, Palacios JM, Probst A, Mengod G. Distribution of Galanin mRNA Containing Cells and Galanin Receptor Binding Sites in Human and Rat Hypothalamus. Eur J Neurosci. 1990;2(7):629-37.
47. Garcia-Falgueras A, Ligtenberg L, Kruijver FP, Swaab DF. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. J Comp Neurol. 2011;519(15):3061-84.
48. Gaus SE, Strecker RE, Tate BA, Parker RA, Saper CB. Ventrolateral preoptic nucleus contains sleep-active, galaninergic neurons in multiple mammalian species. Neuroscience. 2002;115(1):285-94.
49. Suntsova N, Szymusiak R, Alam MN, Guzman-Marin R, McGinty D. Sleep-waking discharge patterns of median preoptic nucleus neurons in rats. J Physiol. 2002;543(Pt 2):665-77.
50. Gong H, McGinty D, Guzman-Marin R, Chew KT, Stewart D, Szymusiak R. Activation of c-fos in GABAergic neurones in the preoptic area during sleep and in response to sleep deprivation. J Physiol. 2004;556(Pt 3):935-46.
51. Anaclet C, Ferrari L, Arrigoni E, Bass CE, Saper CB, Lu J, *et al*. The GABAergic parafacial zone is a medullary slow wave sleep-promoting center. Nat Neurosci. 2014;17(9):1217-24.
52. Bondareff W, Mountjoy CQ, Roth M. Loss of neurons of origin of the adrenergic projection to cerebral cortex (nucleus locus ceruleus) in senile dementia. Neurology. 1982;32(2):164-8.
53. Iversen LL, Rossor MN, Reynolds GP, Hills R, Roth M, Mountjoy CQ, *et al*. Loss of pigmented dopamine-beta-hydroxylase positive cells from locus coeruleus in senile dementia of Alzheimer's type. Neurosci Lett. 1983;39(1):95-100.
54. Busch C, Bohl J, Ohm TG. Spatial, temporal and numeric analysis of Alzheimer changes in the nucleus coeruleus. Neurobiol Aging. 1997;18(4):401-6.
55. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol. 2011;70(11):960-9.
56. Ehrenberg AJ, Nguy AK, Theofilas P, Dunlop S, Suemoto CK, Di Lorenzo Alho AT, *et al*. Quantifying the accretion of hyperphosphorylated tau in the locus coeruleus and dorsal raphe nucleus: the pathological building blocks of early Alzheimer's disease. Neuropathol Appl Neurobiol. 2017;43(5):393-408.
57. Theofilas P, Ehrenberg AJ, Dunlop S, Di Lorenzo Alho AT, Nguy A, Leite REP, *et al*. Locus coeruleus volume and cell population changes during Alzheimer's disease progression: A stereological study in human postmortem brains with potential implication for early-stage biomarker discovery. Alzheimers Dement. 2017;13(3):236-46.
58. Curcio CA, Kemper T. Nucleus raphe dorsalis in dementia of the Alzheimer type: neurofibrillary changes and neuronal packing density. J Neuropathol Exp Neurol. 1984;43(4):359-68.
59. Yamamoto T, Hirano A. Nucleus raphe dorsalis in Alzheimer's disease: neurofibrillary tangles and loss of large neurons. Ann Neurol. 1985;17(6):573-7.
60. Rub U, Del Tredici K, Schultz C, Thal DR, Braak E, Braak H. The evolution of Alzheimer's disease-related cytoskeletal pathology in the human raphe nuclei. Neuropathol Appl Neurobiol. 2000;26(6):553-67.
61. Grinberg LT, Rub U, Ferretti RE, Nitrini R, Farfel JM, Polichiso L, *et al*. The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset? Neuropathol Appl Neurobiol. 2009;35(4):406-16.

62. Goudsmit E, Hofman MA, Fliers E, Swaab DF. The supraoptic and paraventricular nuclei of the human hypothalamus in relation to sex, age and Alzheimer's disease. Neurobiol Aging. 1990;11(5):529-36.
63. Baloyannis SJ, Mavroudis I, Mitilineos D, Baloyannis IS, Costa VG. The hypothalamus in Alzheimer's disease: a Golgi and electron microscope study. Am J Alzheimers Dis Other Demen. 2015;30(5):478-87.
64. Baloyannis SJ, Mavroudis I, Baloyannis IS, Costa VG. Mammillary Bodies in Alzheimer's Disease: A Golgi and Electron Microscope Study. Am J Alzheimers Dis Other Demen. 2016;31(3):247-56.
65. Airaksinen MS, Paetau A, Paljarvi L, Reinikainen K, Riekkinen P, Suomalainen R, et al. Histamine neurons in human hypothalamus: anatomy in normal and Alzheimer diseased brains. Neuroscience. 1991;44(2):465-81.
66. Shan L, Bossers K, Unmehopa U, Bao AM, Swaab DF. Alterations in the histaminergic system in Alzheimer's disease: a postmortem study. Neurobiol Aging. 2012;33(11):2585-98.
67. Chan-Palay VL, Jentsch B. Galanin tuberomammillary neurons in the hypothalamus in Alzheimer's and Parkinson's diseases. Prog Brain Res. 1992;93:263-70.
68. Lim AS, Ellison BA, Wang JL, Yu L, Schneider JA, Buchman AS, et al. Sleep is related to neuron numbers in the ventrolateral preoptic/intermediate nucleus in older adults with and without Alzheimer's disease. Brain. 2014;137(Pt 10):2847-61.