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Chronic sleep deprivation increase the risk of Alzheimer's disease

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ABSTRACT

Introduction: Sleep deprivation is a common phenomenon among modern society. Due to the fact that many people are chronically sleepless, the possible negative consequences of sleep disorders for health should be investigated.
The aim of the study: The aim of this article is to analyze the studies linking sleep disorders with changes in β-amyloid levels and the development of Alzheimer's disease.
Material and method: Standard criteria were used to review the literature data. A search of articles in English was carried out in the PubMed and Google Scholar database.

Description of the state of knowledge: The studies described show that sleep deprivation increases the level of βA in cerebrospinal fluid (CSF) in humans. This suggests that chronic sleep disturbances may contribute to the formation of amyloid plaques and other pathologies found in AD, which leads to an increased risk of this disease.
Summary: The data confirms that sleep provides an important function in maintaining the metabolic homeostasis of neurons, and sleep deprivation significantly raises the level of βA in CSF. However, we still can not tell if a night with sufficiently long sleep can negate the accumulation of β-amyloid caused by poor nocturnal sleep, but this is undoubtedly the direction to be investigated in future years.

Keywords: Sleep deprivation, Alzheimer's disease, dementia

1. INTRODUCTION

Alzheimer's disease (AD) is considered to be the most commonly occuring ailment bound up with dementia (it is estimated that AD is a reason for 60 to 80% of cases of dementia), while the dementic disease alone can be defined as a state implying loss of memory, language, problem solving abilities and cognitive skills which precludes performing everyday activities [1]. The annual morbidity is 2 to 3 cases on every 1000 people in age group 65-69 years and 37-40 cases on every 1000 people among 85-89 year-olds. It is a neurodegenerative, progressive disease which lasts 8-20 years while its clinical symptoms are contained in Global Deterioration Scale [2] and they include an amnesic type of memory impairment, deterioration of language, and visuospatial deficits which in the later stages of the disease imply the necessity of permanent care for the patient.

Extracellular β-amyloid (βA) deposits organised into a form of plaques and intracellular neurofibrillary degeneration formation made out of hyperphosphorylated tau protein seem to be the key stage in the pathogenesis of AD [3]. The pathologies begin to occur about 20 years before the first signs of dementia.

Amyloid precursor protein (APP), physiologically, occurs in intramembranous structures of intraneuronal organelles and in the neurone's cell membrane. It is responsible for the cell adhesion, the axon's growth and synaptic plasticity. Correctly, the APP undergoes cleavage in the amyloid cascade pathway by α-secretase whereas due to the β-site APP-cleaving enzyme (BACE-1 or β-secretase) activity and then γ-secretase enzyme (presenilin) activity it can come to the creation of some isoforms of abnormal βA, from which the βA_{42} form constitutes the main component of the amyloid plaque. The tau protein physiologically is responsible for the microtubules stabilisation while its activity is controlled by its phosphorylation state due to the kinases activity: cyclin-dependent kinase 5 and glycogen synthase kinase 3b (GSK3b), and phosphate removers: phosphatase 2A and 2B [4,5]. In AD patients, the hyperphorsphorylation of the tau protein is observed which precludes its binding to the tubulin disturbs axonal transport and synapses' activity (and creation). The protein is abnormally folded and, as a result, the intraneuronal neurofibrinal bundles occur. In the familial variant of this condition appears APOE gene (coding apolipoprotein E) polymorphism. The ε4 allele of the gene is associated with elevated risk of AD. Apolipoprotein E, binding to βA, creates a complex which is hard to remove from the extracellular matrix [6].

Known risk factors of the disease include age, level of education (mild course of the disease among the patients with longer period of study), solitary life and genetic factors (APOE polymorphism).

The recent studies performed with participation of both humans and animal models suggest the possible mechanism why sleep disorders, interacting with genetic and

environmental risk factors, can contribute to pathogenesis of AD. That why scientists propose the possible model of sleep disorders role and circadian rhythm of βA as a AD risk factor.

2. MATERIALS, METHODS AND AIM

The aim of this article was the analysis of the studies connecting sleep disorders to the changes of β-amyloid concentration and AD progress. All sleep disorders contained in the second edition of the International Classification of the Sleep Disorders (ICSD-2) were taken into consideration.

The standard criteria were adopted for the literature data review. The research for articles in the English language was conducted using the PubMed and Google Scholar base. The following key words were taken into account: Alzheimer's disease, dementia, cognitive disorders, sleep disorders, sleep deprivation. Only full-length articles were analysed. We found 7 articles including the research concerning human populations in 3 different countries. All the articles were published in reviewed journals.

3. SLEEP AND WAKEFULNESS CYCLES

The sleep deprivation associated with increase of work hours at night-time and taking night activities is a common phenomenon of modern society [7]. Sleep and wakefulness are states of activity of the somatic system, occurring cyclically after each other. Reticular system which the main part consist of medullary part of reticular formation in the brain stem, hypothalamus and basal part of prosencephalon are structure responsible for maintaining wakefulness state.

During the wakefulness the highest nervous activity is located in noradrenergic neurons of locus coeruleus and serotonergic neurons of raphe nuclei but cholinergic neurons also have important role in regulation of limbic system and neocortex [8]. Moreover the orexins seem to have a meaning in maintaining wakefulness since deficiency of them can lead to narcolepsy and cataplexy [9]. In the EEG record desynchronized beta waves (frequency over 15 Hz) and synchronized alpha waves (during mental relaxation, amplitude about 50 μV, frequency 8-13 Hz) can be observed in state of wakefulness. Physiologically sleep is not a homogenous phenomenon, it consists of NREM and REM phases which occur alternately. Most likely, it is caused by interaction of the serotonergic and noradrenergic neurons REM-off (which are inactive during REM sleep) and cholinergic neurons REM-on (activate during REM sleep) [10].

The NREM sleep can be divided into four phases occurring after each other which can be distinguished basing on the EEG record: phase I during which alpha waves disappear while the beta waves with low amplitude appears; phase II in which sleep spindles and K-complexes (consisting of a brief negative high-voltage peak followed by a slower positive complex) can be observed; phase III in which delta waves begin to occur; phase IV, so-called delta sleep when only delta waves can be seen [11]. During NREM sleep the most active neurons belongs to solitary tract nucleus, anterior part of hypothalamus, non-specific nucleus of thalamus and basal part of prosencephalon. Adenosine and gamma-aminobutyric acid (GABA) seems to have important role in generating NREM sleep. [11]. In humans, the REM sleep reminds the phase I of the NREM sleep in the EEG record. It is characterized by fast eye movement, muscular atony, dreaming (most commonly unreal). The pontine part of reticular formation of medulla oblongata and a small area in lateral part of tegmentum take part in REM sleep generating. In process of falling asleep an important role plays some substances also known as sleep factors which can be found in cerebrospinal fluid and in the blood. To this sleep factors belongs local hormones and cytokines like: somatostatin, melanocyte-stimulating hormone, adenosine, insulin, cholecystokinin, bombesin, prostaglandin E2, interleukin-1, interleukin-6 and tumor necrosis factor alpha [12].

It is believed that the role of sleep is to provide efficiency during wakefulness through regeneration of insufficiently stimulated synapses, maintaining plasticity of neurons, temperature reduction, energy save, optimal functioning of immunologic system and memory consolidation.

Nowadays, three kinds of sleep disorders can be distinguished: insomnia (difficulties in falling asleep, awakening during sleeping or premature awakening), excessive sleepiness which can be primal (as a narcolepsy) or symptomatic (for example during dementia, after an injury or in case of elevated intracranial pressure) and parasomnias third form of sleeping disorders, which include somnambulism, night terrors, sleep paralysis [13].

4. SLEEP DEPRIVATION IN ALZHEIMER DISEASE

Some patients with AD (25-30%) have sleep deprivations in the form of insomnia, sleepiness during the day, reversal sleep-awake daily cycle. [14]. The observation of patients shows, that sleep disorders may be connected with neuropsychiatric deprivations such as delusions, aggression, or anxiety disorders. Pure sleep disorders may occur in AD 10–15 years before other clinical symptoms of AD.

In patients with dementia, sleep deprivations may appear even in every second person (40-50%). They can be seen as hypersomnia (50,1%), insomnia (49,9%), rapid eye movement sleep behavior disorder (RBD) (22,6%) and in restless legs syndrome (RLS) (6,1%). Most frequently primary cause of sleeping disorders are sleep related breathing disorder (SRBD), in which 90 % of it is a sleep apnea (OSA) and 10 % is a upper airway resistance syndrome (UARS). These are common in obesity patients. The evidences from studies show that SRBD and RLS are seen in patients with agitation behaviors [15,16].
Detection of any kind of sleeping disorders connected with breathing problems is so important because it can cause hypoxemia and in consequence neurodegeneration.

Patients with AD usually have shorter sleep then healthy population. Additionally the sleep quality is significantly lower. Moreover slow wave sleep (SWS) and REM phase can be significantly shorter or may even completely disappear in those conditions. Nocturnal agitation and inability of sleeping may be connected with daily naps which are common for patients with AD [17].

Sleep disorders do not afflict only AD patients. With age, most people develop physiological sleep disorders associated with the aging of the body. The causes can be divided into those that man creates himself, with his behavior - for example, short afternoon naps may lengthen during life, and this may decrease sleepiness at evening. Furthermore, sleep disorders can be associated with damage of the optic nerve or the ganglion cells responsible for the perception of light and afferent information to the brain about necessity of secretion of melatonin. The disturbed mechanism of circadian rhythm control - damage to the suprachiasmatic nucleus in the hypothalamus (mainly noradrenergic nerve connections) could be another reason of sleeping disorders. Hormones can also have a significant impact on sleep deprivation. It turns out that in older age there is an increased level of cortisol in blood which makes falling asleep more difficult than in patients with normal cortisol blood concentration [18]. There is also thesis about the change in body temperature of older people which increases in the morning hours and may cause disturbances in sleep-awake rhythm [19].

Most changes in sleep disorders, to which the above-mentioned causes can lead, appear around the age of 60 [20]. Considering that at the age of 60 every hundredth person will become ill with AD, and at the age of 85 one of every ten person, we can reach the conclusion that sleep disorders appears often than other symptoms which does not mean they herald the upcoming illness.[21]

There are studies in which the incidence of sleep disorders in patients with AD was checked, in comparison to healthy control groups. One of the studies found that in AD

patients the overall incidence of sleep disorders and disturbances in nocturnal activity was 1.16, where in the control group this frequency was 0.76 [22].
Progression of Alzheimer disease cause decreasing of the level of melatonin in the cerebrospinal fluid. In addition to its "sleeping" action, melatonin also acts as an antioxidant and a neuroprotector against oxidative stress and amyloid toxicity. This means that falling melatonin level can be a reason of sleep disorders in patients with AD and this condition will aggravate disease per se. Moreover, a reduced level of melatonin was observed in preclinical AD, which may be an important marker of the disease to detect it in early stages [23].

There are studies which point the thinner retinal fiber layer (RNFL) in patients with AD compared to the elderly people with mild cognitive impairment and healthy control group. RNFL is respectively risen in these three groups. So there may be some correlation between AD and the thickness of RNFL. J. Kwon et al. in his work suggests that the thickness of RNFL may be a good indicator of the measurement of early stages of the AD [24]. What is more, the thickness of RNFL causes worse sight, what may also be connected to the worst perception to the light and then with worst circadian rhythm of the patients day and then with sleep deprivations.

5. SLEEP DISORDERS, THE LEVEL OF β-AMYLOID AND TAU PROTEIN AND THE RISK OF ALZHEIMER'S DISEASE

Despite evidence that lack of sleep raises β-amyloid levels in the mouse interstitial fluid [25, 26, 27], there is a few information about impact of depriving a sleep to the β-amyloid level in the human brain. Studies which show that sleep deprivation increases the level of βA in the cerebrospinal fluid (CSF) in humans, suggest that chronic sleep disorders may contribute to the formation of amyloid plaques and other pathologies occurring in AD, resulting in an increased risk of this disease. To date, studies have not investigated which aspect of sleep modulates βA or other biomarkers of Alzheimer's disease.

Table 1. Characteristics of the reviewed research showing the relationship between sleep disorders and levels of βA in CSF

Study	Country	Study group	Age (years)	Tests	Results
S. Ooms et al. (2014)	Netherlands	26	40-60	polisomnography; βA in CSF	βA42 in CSF o 6% higher in the research group
C. Benedict et al (2015)	Sweden	2322	50-88	βA in CSF; questionnaires assesing sleep and cognitive function	1,33-x higher risk of dementia sleep-deprived group
Y. Ju et al. (2017)	USA	17	35-65	actigraphy; polisomnography; βA, tau, YKL-40, hipocretin, total protein in CSF	βA in CSF 10% higher in the research group
M. Wei et al. (2017)	USA	20	23-30	βA, sLRP-1, sRAGE, SOD and MDA in urine	βA40 in plasma 32% higher after sleep deprivation
M. Olsson et al. (2018)	Sweden	13	20-40	aktygrafia; polisomnografia; βA, orexins, biomarkers of astrocytes and microglia in CSF	oreksyna in CSF 27% higher after sleep deprivation
D.W. Chen et al. (2018)	USA	56	43-67	βA, tau in CSF	βA 42 in CSF 12% higher in chronic sleep disorder group
E. Shokri-Kojori et al. (2018)	USA	20	22 -72	PET	increase βA in the right hippocampus and in the thalamus after sleep deprivation

One of the first studies assessing the effect of sleep disorders on the concentration of βA peptide was published in 2014 [28]. 26 healthy men aged from 40 to 60 years were randomly assigned to the study group (n = 13) which spent 1 night with complete sleep deprivation, or control group (n = 13) which spent one night with unlimited sleep. The sleep was monitored by polysomnography, and in the morning, cerebrospinal fluid was collected by lumbar puncture to determine the concentrations of βA. It was found that in the study group, βA42 concentrations were on average 6% higher than in the control group. This allowed the hypothesis that chronic sleep deprivation increases βA levels in the brain, which increases the risk of Alzheimer's disease. The results of this research initiated further studies analyzing the relationship between sleep deprivation and β-amyloid levels and dementia disorders.

In 2015, C. Benedict et al. published the results of a 40-year follow-up, in which the relationship between sleep disorders and the risk of dementia, including AD, was examined. The study involved 2322 healthy men aged 50 who were evaluated again at the age of 60.70, 77, 82 and 88 years. Each time, the concentration of βA in CSF, sleep hygiene and the risk of dementia were evaluated using standardized questionnaires. Cox multivariate regression analysis using the current exposure and covariate showed that men with self-reported sleep disorders had a ~ 1.33-fold greater risk of developing dementia during the 40-year follow-up

period compared to men without them. In addition, this relationship was most pronounced in the case of AD [29].

A group of scientists from Washington University assessed how sleep disorders affect the level of β-amyloid and tau protein in the cerebrospinal fluid [30]. The research team carried out a study involving 17 healthy adults between the ages of 35 and 65 who never reported sleep disorders. Each examined person wore an actigraph on the wrist for several days. The device recorded the activity of the subject during the day and night, thanks to which the length of latency of sleep, total length of sleep, the number of awakenings during sleep and the amount of time actively spent during the day were measured. After spending a dozen or so days with the actigraph, the participants were examined by a night-time polysomnography recording the reading of EEG, ECE, EEA and EMG. Half of the volunteers were randomly assigned to a group whose members were intentionally awakened several times at night as soon as they fell into a deep sleep. In the second half, participants sleep was not interfered with. Each of the study subjects underwent a lumbar puncture in the morning to acquire CSF in which the levels of β-amyloid, tau protein, total protein, YKL-40 (marker of inflammation of the nerves) and hypocretin were determined. A few weeks later, the entire procedure was repeated, replacing the participants with the group. Those who had previously slept without a break were waked up and vice versa. It turned out that compared to a normal night's sleep, after the night when sleep was disturbed, the level of βA in volunteers' CSF was 10% higher. There was no similar increase in tau protein. However, in the group of subjects who have been experiencing sleep problems during the week preceding the study according to the reading of the actimeter, tau levels have been elevated.

M. Wei et al. recruited 20 volunteers aged 23-30 with normal cognitive function and no sleep disorders in history [31]. Participants underwent 24-hour sleep deprivation. Then blood samples were taken to determine βA, sLRP-1, sRAGE, SOD and MDA. Sleep deprivation was shown to increase plasma βA40 levels by 32.6% compared to pre-test concentrations, but decreased sLRP1, sRAGE and SOD concentrations. A positive relationship was found between the duration of sleep deprivation and the level of βA40 in plasma.

In 2018, results of two similar studies were published. In the work under the supervision of M. Olesson, the participants of the study were 13 healthy adults between the ages of 20 and 40 years [32]. First, they spent 5 nights with an 8-hour sleep, and then 5 nights with a 4-hour sleep. After this period, CSF was collected and levels of βA, orexin and biomarker derived from astro and microglia were determined. It was found that partial sleep deprivation was associated with a 27% increase in the concentration of orexin in the cerebrospinal fluid. D.W. Chen et al. compared patients with chronic insomnia to healthy individuals for the concentration of βA and tau protein in CSF and other pathological features in the pathogenesis of AD [33]. 23 patients aged from 46 to 67 were recruited to the first group, and 23 volunteers aged 43 to 67 were included in the healthy group. It was found that the concentration of βA42 in CSF was increased by 12% in patients with chronic insomnia compared to healthy subjects. In addition, it was noted that the levels of βA40 and βA42 in CSF are significantly correlated with the quality of sleep.

Another research group evaluated brain regions with elevated β-amyloid levels after sleep deprivation. Twenty healthy volunteers aged 22 to 72 years were evaluated for the study [34]. Each person had a FBB-PET examination performed after a full night's sleep and after a night without sleep. A study using positron emission tomography imaging was to visualize the areas of the brain with the highest β-amyloid burden. The study showed that after one day of sleep deprivation, an increase in the level of β-amyloid in the right hippocampus of the brain, as well as in the thalamus, noticed. Hippocampus is a region of the brain associated with long-term memory, and thalamus is responsible, among others, for sensory information processing.

It was found that the radiologial imaging findings of this study are similar to those of the very early stages of Alzheimer's disease. In addition, the hippocampus is considered to be the most sensitive region of the brain for AD neuropathology. Using positron emission tomography, it has been shown that acute sleep deprivation affects β-amyloid load in regions of the brain that are associated with Alzheimer's disease.

The before mentioned studies confirm that sleep provides an important function in maintaining the metabolic homeostasis of neurons. However, it is still unclear which sleep phase exactly has the greatest impact on modulation of the βA level in the interstitial fluid occurs.

β-amyloid is released into the interstitial space during the activity of synaptic neurons [35]. In contrast, the clearance of substances dissolved from the interstitial space, including β-amyloid, is accelerated during the sleep rich in delta waves, specific for REM sleep [36]. Clinical studies have also shown that the levels of βA in the cerebrospinal fluid are highest before bedtime and the lowest after waking up [28].

This information suggests that interruption of REM sleep may result in increased neural activity, and therefore increased β-amyloid release and reduced clearance of the substance in the cerebral fluid, which may lead to an increased level of βA in the cerebrospinal fluid [37].

Studies in mice prove that chronic sleep disorder, apart from changes in βA, increases tau protein levels and its phosphorylation [38, 39]. Tau protein is also released during neuronal activity, although its brain clearance is slower than for β-amyloid [40].

Sleep deprivation is also positively correlated with the concentration of free radicals. In the central nervous system, they accumulate especially in the hippocampus and the locus coeruleus. The influence of oxidative stress in the pathomechanism of AD can be explained as an effect on the metabolism of amyloid or tau protein. What's more, oxidative stress can cause nerve cell debris, which may contribute to the higher risk of developing AD. Increased sleep deprivation also leads to a decrease in sirtuin activity, which is responsible for increasing the activity of superoxide dismutase and NADH dehydrogenase by direct interaction with them.

Most of the studies described in this article assess the consequences of sleep disorders during one or several nights. Such a short period has no major impact on the development of Alzheimer's disease. The levels of β-amyloid and tau protein in CSF probably return to the neutral level after a full night's sleep. However, the problem may be significant in people who experience chronic sleep disorders. In this situation, there may be a constantly elevated level of Alzheimer's disease proteins and, as a result, an increased risk of amyloid plaques forming in the brain and AD.

6. SUMMARY

As we know, Alzheimer's disease is closely related to the deposition of amyloid deposits in the brain. Under their influence, the disappearance of neurons and synaptic connections appears. Physiologically during the day, the amount of amyloid is much higher than at night. This is associated with a more intense removal at night. At the moment when sleep disorders start to occur, there is no difference in the amount of amyloid between night and day.

As with amyloid, the accumulation of tau protein is involved in the pathogenesis of AD. Studies on animal models have shown that those with sleep disorders have elevated levels of CSF tau protein and learning and memory disorders.

About every second adult reports that the quality of their sleep at night is insufficient. In addition, insomnia and reduced sleep quality are typical symptoms of many common diseases in modern societies (eg diabetes, hypertension and obesity). Due to the fact that many people are chronically sleepless, the possible negative consequences of sleep disorders

for health should be investigated. In recent years, there has been a particularly strong relationship between sleep disorders and an increased risk of AD. Although, today, studies have shown that sleep deprivation significantly raises the level of βA in CSF, we still can not tell if a night with sufficiently long sleep can negate the accumulation of β-amyloid due to bad nocturnal sleep, but this is undoubtedly the direction to be investigated in future years.

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