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Plasma Amiloid β42 in Patients with Obstructive Sleep Apnea before and after CPAP-Therapy: Pilot Study

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Abstract

The aim of this pilot research was to assess the sleep fragmentation influence on amyloid β42 (Aβ42) plasma levels before and after CPAP in patients with obstructive sleep apnea (OSA).

Materials and Methods: The study involved 24 patients (mean age of 52.5±2.7 years) with OSA and 20 persons without OSA (mean age of 49.1±8.2 years). All participants underwent overnight polysomnography, The Aβ42 level was determined in blood plasma by an immunoassay method. Patients with OSA were treated with auto-CPAP for 3 months.

Results: The research showed the following results in patients with OSA before CPAP, as compared to control: sleep fragmentation 1–2 times, increases in non-rapid eye movement sleep stage by 60% ($P<0.05$) and arousal index by 55% ($P<0.05$), and decreases in slow-wave sleep duration by 40% ($P<0.05$) and rapid-eye-movement sleep by 43% ($P<0.05$). After CPAP-therapy, a decrease in arousal index by 40% ($P<0.05$) and apnea/hypopnea index ($P<0.05$), and increases in oxygen saturation by 17% ($P<0.05$), the slow-wave sleep duration by 56% ($P<0.05$) and rapid-eye-movement sleep by 55% ($P<0.05$) were found. Aβ42 levels were significantly lower in the group with OSA before CPAP-therapy, as compared to the control group and the group with OSA after CPAP-therapy ($P<0.05$). There were no differences in Aβ42 levels after treatment between control and main group.

Conclusion: Moderate and severe OSA is associated with a decrease in Aβ42 plasma level. CPAP-therapy leads to increase this peptide in blood plasma. (**International Journal of Biomedicine. 2019;9(3):205-209.**)

Key Words: obstructive sleep apnea • continuous positive airway pressure • polysomnography • amyloid β42

Abbreviations

AHI, apnea/hypopnea index; **AD**, Alzheimer's disease; **AI**, arousal index; **BMI**, body mass index; **CPAP**, continuous positive airway pressure; **NREM**, non-rapid eye movement; **OSA**, obstructive sleep apnea; **PSG**, polysomnography; **REM**, rapid-eye-movement; **SWS**, slow-wave sleep.

Introduction

Obstructive sleep apnea (OSA) is a condition characterized by repeated episodes of complete (apnea) or partial (hypopnea) obstruction of the upper respiratory tract during sleep. Its prevalence varies from 14.7% to 36.5% and depends on gender and nationality.[1] It has been found that OSA is associated not only with daytime sleepiness, nocturnal enuresis, cardiovascular diseases, and insomnia, but also with early neurodegenerative changes, such as impairment of memory, attention, ability to learn, and intellectual activity.[2-6] There is a great deal of data about the relationship between OSA and AD.[7,8]

It is possible that a decrease in SWS time and chronic hypoxia are among the main factors in the development of

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cognitive impairment in OSA patients.[9] Moreover, it has been shown that SWS duration is associated with intracellular aggregation of amyloid β42 (Aβ42) peptide in the neocortex.[10] This peptide can form so-called amyloid plaques consisting of peptide clusters rolled up in the form of beta-folds. The Aβ42 peptide can also form oligomers that trigger chain reactions of the amyloid plaques and tau-proteins formation by the prion mechanism.[11] Currently, cerebrospinal fluid Aβ42 is a biomarker of AD in clinical practice. Although determining Aβ42 in the blood is a less invasive intervention, there are few studies of this marker in blood plasma.[12-15] Aβ42 plasma level can be demonstrated not only in the brain, but also in peripheral tissues because it has been shown that this peptide's metabolism can be in those tissues.[16]

CPAP-therapy[17] is the gold standard for OSA treatment. We hypothesized that CPAP-therapy would not only lead to improvement in OSA, fewer arousals during the night, and increasing SWS duration but also would change Aβ42 plasma blood levels. Thus, the aim of this pilot research was to assess the sleep fragmentation influence on Aβ42 plasma levels before and after CPAP in patients with obstructive sleep apnea.

Materials and Methods

The study involved 24 patients (14 men and 10 women) attending the Somnology Center of the Scientific Center for Family Health and Human Reproduction Problems (Russian Federation, Irkutsk) with complaints of snoring and respiratory arrest during sleep. The average age of the studied patients was 52.5±2.7 years

Inclusion criteria were age between 45 and 60 years and a clinical diagnosis of moderate and severe OSA, as defined by the American Academy of Sleep Medicine criteria.[17] Exclusion criteria were previous treatment for OSA with CPAP or surgery, history of a motor vehicle accident related to sleepiness within the past 12 months, presence of chronic medical conditions, and shift work.

The study was approved by the Scientific Center of Family Health Problems and Human Reproduction Ethics Committee. Written informed consent was obtained from each patient.

According to the study design, 20 people (12 men and 8 women) (mean age of 49.1±8.2 years) who did not snore were included as a control group. PSG was performed in the control group and in patients with OSA before and after CPAP. Characteristics of participants are presented in Table 1. The groups were generally similar in mean age, sex and BMI.

Overnight polysomnography

The polysomnographic monitoring was carried out in a specially equipped room, which was as close as possible to the conditions of a bedroom, using the GRASS-TELEFACTOR Twin PSG (Comet) system with an As 40 amplifier with the SPM-1 (USA) integrated sleep module, according to the standard methodology. We evaluated overnight 16-channel polysomnography with 2 electroencephalograms (C4,C3,O1,O2), 2 electrooculograms (ROC, LOC) and 2 electromyogram channels; oral/nasal airflow by thermistor; respiratory effort via conductance belts on chest and abdomen; snoring sounds via microphone; oxygen saturation via pulse oximeter. Each 30-sec epoch was manually scored using standard scoring criteria supplemented by apnea-hypopnea criteria, according to American Academy of Sleep Medicine recommendations.[17]

OSA is classified as mild (AHI: 10–15 events per hour), moderate (AHI: 15.1–30 events per hour) and severe (AHI >30 events per hour).[17]

CPAP- therapy

Patients with OSA were treated with auto-CPAP (Prisma 20, LÖWENSTEIN MEDICAL, Germany). CPAP machines and masks were donated by official and exclusive representative LÖWENSTEIN MEDICAL in Russia (Spiromedical Company). All patients used auto-CPAP for >4 h/night for 3 months with a nasal mask (10 patients) and oronasal mask (4 patients). Compliance was 65-100%.

Blood tests

The Aβ42 level was determined in blood plasma. Venous blood was sampled after, 12h of overnight fasting, into tubes with EDTA between 8:00 and 9:00 a.m. after polysomnographic testing. Samples were centrifuged for 10 min at 1.500g at 4°C. Samples were kept frozen at 80°C for up to one month. The Aβ42 content was determined by an immunoassay method using commercial sets Amyloid-beta (1-42) High Sensitive ELISA on the EL×808 Micro Plate Reader. Measurement range: 1.56-100 pg/ml (0.35-22.17 pmol/L, as molecular weight of Aβ (1-42) in EDTA plasma).

Table 1.

Basic and PSG characteristics in control and patients with OSA before and after CPAP-therapy

Parameters	Control group (1)	OSA before CPAP-therapy (2)	OSA after 3-month CPAP-therapy (3)	$P<0.05$
Age (yrs)	49.1±8.2	52.5±2.7	52.5±2.7	-
Sex (male, %)	12(60%)	14(58.3%)	14(58.3%)	-
BMI (kg/m^2)	27.3±1.5	30.2±4.8	30.2±4.8	P_{1-2} P_{1-3}
Sleep efficiency (%)	97.1±1.9	85.1±3.3	98.3±1.7	P_{1-2} P_{1-3} P_{2-3}
WASO (min)	16.6±10.2	13.3±1.5	4.51±3.10	P_{1-2} P_{1-3} P_{2-3}
TST (min)	429.5±26.1	423.1±20.9	431.6± 19.8	-
$NREM_{1-2}$ (min)	157.7±10.8	252.1±37.4	188.4±20.1	P_{1-2} P_{2-3}
$NREM_3$ (min)	145.2±8.2	87.3±31.2	136.5±11.4	P_{1-2} P_{2-3}
REM (min)	143.3±14.1	81.4±42.1	125.9±21.4	P_{1-2} P_{2-3}
AHI (events/hour)	3.89±1.35	38.6±18.2	4.04±1.97	P_{1-2} P_{2-3}
AI (events/hour)	33.1±14.3	51.2±12.0	39.7±21.2	P_{1-2} P_{2-3}
SaO_2 (%)	96.7±1.2	80.4±5.1	94.3±9.8	P_{1-2} P_{2-3}

WASO - wake time after sleep onset, TST – total sleep time, $NREM_{1-2}$ - NREM stage 1-2, $NREM_3$ - NREM stage 3, SaO_2 - oxygen saturation

Statistical analysis was performed using STATISTICA 6.1 software (Stat-Soft Inc., USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±standard deviation for continuous variables. For data with normal distribution, inter-group comparisons were performed using Student's t-test. Differences of continuous variables departing from the normal distribution were tested by the Mann-Whitney U-test. A probability value of $P<0.05$ was considered statistically significant.

Results and Discussion

This research showed the following results in patients with OSA before CPAP, as compared to control: sleep fragmentation 1–2 times, increases in NREM sleep stage by 60% ($P<0.05$) and AI by 55% ($P<0.05$), and decreases in SWS duration by 40% ($P<0.05$) and REM sleep by 43%($P<0.05$). After CPAP-therapy, we found a decrease in AI by 40% ($P<0.05$) and AHI ($P<0.05$), and increases in oxygen saturation by 17% ($P<0.05$), the SWS duration by 56% ($P<0.05$) and REM sleep by 55% ($P<0.05$).

Aβ42 levels were significantly lower in the group with OSA before CPAP-therapy, as compared to the control group and the group with OSA after CPAP-therapy ($P<0.05$). (Fig.1) There were no differences in Aβ42 levels after treatment between control and main group. Thus, moderate and severe OSA is associated with a decrease in Aβ42 plasma level. CPAP-therapy leads to increase this peptide in blood plasma.

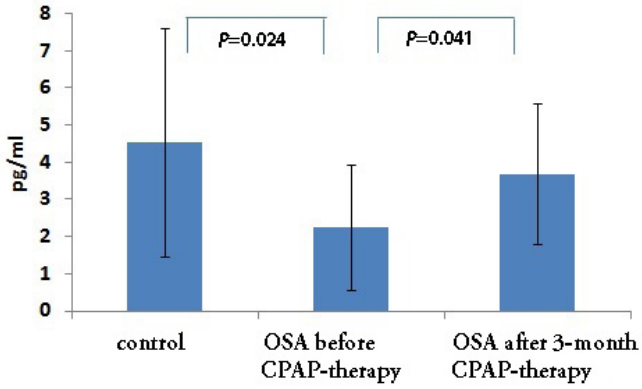

Fig. 1. *Aβ42 plasma levels in control group and patients with OSA before and after CPAP-therapy.*

Currently, new approaches to the study of OSA and some markers of cognitive impairment are being developed in sleep medicine. It has been found that the brain's biochemical wastes, including Aβ42, are removed through the glymphatic system. The glymphatic network serves as a "front end" for waste clearance, and is connected downstream to an authentic lymphatic network, associated with *dura mater* covering the brain, as well as cranial nerves and large vessels at the skull exits. However, the anatomical and functional interconnections between these two networks are still not completely understood.[18] The results of some studies have demonstrated that during sleep, the cerebrospinal fluid flows more profusely and the elimination of toxic substances from neurons and intercellular spaces is greatly increased. Thus, the glymphatic system is more active during sleep than during wakefulness.[19,20] The reason for this is increased synaptic plasticity during SWS.[21,22] Thus, sleep plays an important role in the elimination of unwanted by-products, including Aβ42, from the brain; and sleep fragmentation in patients with OSA can lead to waste accumulation in the brain and formation of plaques. At the same time, it has been shown that sleep extension decreases plaques in animal models.[23]

It is possible that intermittent hypoxia in OSA can lead to changes in the permeability of the blood-brain barrier, deterioration of synaptic plasticity and the development of subsequent cognitive impairment.[24] The results of experimental studies have shown that violation of the integrity and increased permeability of the blood-brain barrier during chronic and prolonged intermeeting hypoxia and pronounced sleep fragmentation contribute to an increase of the Aβ42 level in the blood plasma.[25,26] Despite the large number of studies on determining Aβ42 levels in cerebrospinal fluid, it has been shown that determining Aβ42 plasma levels is also possible not only in patients with AD,[14,15,27] but also in patients with OSA.[13] Thus, it has been shown that Aβ42 plasma level in adolescents with OSA is higher than in the control. Moreover, a positive correlation between Aβ42 and AHI was found. This tendency remains even after a tonsillectomy with the elimination of hypoxia and improvement of the sleep structure.[13] The results of our research, however, are contrariwise; they demonstrated that the Aβ42 plasma level in patients with OSA is lower than in control. It is possible that this because of age differences of the participants in the two studies. It is known that several zinc-proteases, such as neprilysin, its homologues neprilysin 2 and the endothelin converting enzymes 1 and 2, regulate some neuropeptides and are the main beta-amyloid-degrading enzymes. During the ageing process, the expression and activity of these metallopeptidases decline, which leads to an Aβ42 clearance deficit and its accumulation in the brain. Some of these changes in the properties of the enzymes are due to their reduced expression and/or structural modification by reactive oxygen species.[28]

In addition, the results of experimental studies have demonstrated that hypoxia leads to a decrease in neprilysin activity.[29,30] It has been shown that neprilysin mRNA and expression of protein levels is decreased in the primary cortical and hippocampal neurons of mice after hypoxic treatment. It has also been found that there is an increase in histone H3-lysine9 demethylation and a decrease in H3 acetylation in the neprilysin promoter regions following hypoxia, and that hypoxia causes up-regulation of histone methyl transferase G9a and histone deacetylases HDAC-1.[30] Thus, frequent hypoxia does not allow Aβ42 degradation and its transport in the blood. The proof of this can be seen in the results of our pilot research, which demonstrated a decrease in the plasma peptide level in OSA patients.

In addition, patients experienced an improvement of sleep structure and an increase in Aβ42 plasma level after

CPAP-therapy for 3 months. It is possible that an increase in the time of SWS leads to elimination of pathological proteins to the blood and does not allow the formation of "sludge" and pathological amyloid plaques.

Thus, our results confirm the "drainage" function of the brain during SWS and show that poor elimination of Aβ42 from the brain in OSA patients suggests a possible prediction of the early development of AD in such patients. Of course, these results are preliminary and require further confirmation. If future studies confirm these data, sleep monitoring can be a simple and affordable way to detect AD early.

Competing Interests

The authors declare that they have no competing interests.

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