

Original Article

Global Cognitive Performance and Assessment of Memory Functions in Obstructive Sleep Apnea

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Abstract

Introduction: Cognitive problems in patients with obstructive sleep apnea have been suspected since the 1980s. Several studies have investigated different cognitive domains. A similar widespread survey has not been done in the Bulgarian population.

Aim: This study aimed to evaluate global cognitive functioning and memory function in patients with obstructive sleep apnea and to examine the potential influence of comorbidities on cognitive functions.

Materials and methods: The study examined the neurocognitive profile of 103 consecutive patients newly diagnosed with OSA and 31 healthy controls. A list of inclusion and exclusion criteria was developed. Sleep breathing was examined in both groups. The other methods were: a medical history of patients, clinical examination, neuropsychological assessment, statistical analysis.

Results: The study found that the global cognitive functioning of patients with OSA and the memory function was impaired. Shortterm memory has been found affected predominantly. Only obesity was distinguished as a major factor relevant to the severity of cognitive changes in the study group. A statistically significant difference between the groups with and without obesity was found for the applied memory tests, except for the delayed recall and word recognition. The duration of exposure to hypoxia and sleep fragmentation is important for the severity of cognitive deficits. The results confirmed this theory showing that this factor is among the major severity factors.

Conclusion: The study found that the global cognitive functioning of patients with OSA, as well as memory function, were impaired. The role of comorbidities is complex and far from clear.

Keywords

global cognitive performance, memory, obstructive sleep apnea

INTRODUCTION

A well-documented fact is that obstructive sleep apnea (OSA) may cause marked daytime sleepiness, mood disturbance, fatigue, poor quality of life, and depressive symptoms.¹ The link between cognitive symptoms and OSA was established in the 1980s. The first studies conducted in this field showed that some domains were affected and others were not²⁻⁴, and some studies rejected the presence of impairment of cognitive skills.⁵ The explanation for the deficit was given by Beebe & Gozal⁶, who put two phenomena at the center of their theory: sleep fragmentation and hypoxemia, which lead to deficits in executive functions and other cognitive spheres. Sleep fragmentation is a disturbance of normal sleep architecture (interruption of sleep cycles) due to frequent arousal caused by sleep apneas and hypopneas.

The effects of OSA on global cognitive performance are not explicit, Decary et al.7 describe deterioration, while Aloia et al.⁸ and Beebe et al.⁶ do not confirm it. The term 'memory impairment' is nonspecific and may reflect a variety of problems. It is most commonly used for episodic memory impairment. Even in this particular case, the 'memory impairment' could be due to affecting each of the sequential steps required to learn new information - registration, coding, storage, and recall. Registration is a function of attention, which helps to extract information from the sensory cortex. It is impaired in conditions affecting attention processes such as depression, anxiety, sleep disorders, and use of benzodiazepines. In these cases, the information cannot be adequately recorded and the subsequent recall will be violated, not because of a significant memory deficit, but because of impaired attention. The encoding and subsequent storage of information is a transformation of registered stimuli into memory traces. After processing in the primary and associative sensory cortical fields, the information enters the neural circuit of Papez (the hippocampus-mammillothalamic circuit), where it is transformed into memory traces. In the case of bilateral hippocampal damage, the information cannot be stored in long-term memory and therefore cannot be reproduced. This type of disorder is defined as a true memory deficit. Recalling of already encoded and stored information depends on the ability to activate retrieval strategies and it is a function of the frontal lobes.⁹ An impaired recall is observed in subcortical dementia, as well as in functional conditions such as depression and normal aging. The best method for understanding the etiology of a memory disorder is an objective test for evaluating verbal episodic memory, such as the Free and Cued Selective Reminding Test (FCSRT), which controls attention processes and facilitates recall, allowing separate assessment of registration, coding and the storage and recall of information.¹⁰

In 2003, Beebe et al.⁶ published a meta-analysis examining the neuropsychological effects of untreated OSA. The research concludes that OSA does not impair intelligence as a whole or verbal memory, but it does affect vigilance and executive functions. In their meta-analysis, episodic memory is first divided into visual and verbal domains, then into short- and long-term memory. Short-term memory is measured by repeating information presented once or presented in multiple trials, and long-term memory is measured by repeating information after the time of presentation. Besides, the initial separation of verbal and visual subgroups leads to several discrepancies in the analysis of the results. Episodic memory tasks have the following parts - immediate repetition, repetition after several attempts, delayed repetition, and recognition. Immediate repetition evaluates the capacity of short-term memory to encode information after only one attempt. The assessment of the result after several trials evaluates the ability to learn information between trials. Delayed repetition gives information about the ability to withhold information after a certain period. Recognition tasks measure retained information with a task with presenting the original stimulus among other elements. In case of disturbance of both repetition and recognition, means that the information has not been encoded. When there is a lack of recognition impairment with a deficit in immediate and delayed repetition, it means that either the information has been encoded but not completely, or that the retention and storage are insufficient of information.

AIM

The primary aim of this study was to look for an association between OSA and the presence of impairments in global cognitive functioning and memory. The secondary aim of the study was to examine the potential influence of comorbidities on cognitive functions.

MATERIALS AND METHODS

The study examined the neurocognitive profile of 103 consecutive patients newly diagnosed with OSA and 31 healthy controls.

Inclusion criteria: Apnea hypopnea index (AHI)> 5 on respiratory polygraphy in the presence of one or more of the following symptoms: daytime sleepiness, snoring, family history of pauses in breathing or waking due to choking or gasping, diagnosed arterial hypertension, ischemic heart disease, heart failure, atrial fibrillation, type II diabetes mellitus, mood fluctuations, and cognitive deficits. AHI is derived from the total number of apneas and hypopneas divided by the total sleep time. Apnea is defined as the cessation of airflow for at least 10 seconds with persistent respiratory effort when the apnea is central. Hypopnea is a decrease by 30% or more in flow lasting at least 10 seconds and associated with a 4% or greater oxyhemoglobin desaturation. Age between 18-65 years.

Exclusion criteria: Presence of cognitive deficit before the diagnosis of OSA due to neurological or somatic disease; presence of pathology from otorhinolaryngological examination excluding OSA.

The control group also had a sleep breathing examination. A cohort of AHI <5/hour was selected, matching the patient group by gender, age, and educational level.

Methods of study

Diagnosis of the disease by examining sleep breathing

Patients were diagnosed by the recommendations of the AASM for the evaluation, testing, and treatment of patients with obstructive sleep apnea by conducting a respiratory

Recording is analyzed by automatically determining a minimum oxygen saturation (Min Sat O_2), and oxygen desaturation index (ODI), respiratory events are analyzed, and the apnea-hypopnea index (AHI) is calculated based on which, patients are divided into three groups: patients with mild OSA (AHI-5-14), moderate OSA (AHI-15-29) and severe OSA (AHI \geq 30).

Taking a medical history of patients

A detailed history was taken from patients aiming at learning the characteristics of sleep, daily symptoms, accompanying diseases, and presence of bad habits in them.

Clinical examination

Physical examination was performed, neurological status was taken and some anthropometric indicators were measured as predictors of the disease, such as height, weight, waist, neck circumference, BMI calculation.

Neuropsychological assessment with a battery of tests to assess fatigue, sleepiness, depression and cognitive tests. They are administered to patients in the same time range. The cognitive assessment includes: MMSE (Mini-Mental State Examination) is a widely used screening test to evaluate global cognitive functioning in clinical settings introduced by Folstein et al. in 1975. The scale examines time and place orientation, working memory, attention, episodic memory, language skills, and constructive praxis. A maximum of 30 points is the overall score. It should be noted that the results of the MMSE test are highly dependent on age and level of education.¹¹

The original English version of MMSE has been trans-

lated into Bulgarian by Prof. Lachezar Traykov and Assoc. Prof. Margarita Raycheva with minimal changes in verbal stimuli. It was validated in 2013 in Bulgaria by M. Raycheva, K. Stoyanova, A. Dzhanyan, S. Mehrabian, R. Pavlova, M. Petrova, and L. Traykov.¹²

Word List Recall Test

The Word List Recall test is a memory task evaluating the memory process with the repetition of a list of words. A list of 10 commonly used, picturesque words are read at a steady pace - 1 word every 2 seconds. Immediate recall is the first task; the patient is then instructed to repeat all the words he has memorized. When the patient could not repeat any more words, he goes on to read the words again and repeat the memorized ones. Three attempts are made and after the last one, the patient is instructed to memorize the words, because after a while he will be asked again to repeat the memorized ones. In the case of a delayed recall, the patient is instructed after a while to spontaneously say all the words he remembers from the three times read list. The last element of this test is the late recognition of words. The list of words and ten new words are presented to the patient. The words are read aloud at the same pace, asking the patient after each word whether it has been presented in the previous reading of the words. The patient goes to the next word after answering 'yes' or 'no'. The Word List Recall is most commonly used in evaluating episodic memory.¹³ Whether immediate recall, delayed recall or recognition suffers gives information which of the three memory processes is analyzed: fixation, reproduction, and retention. The Bulgarian translation of this test is by Prof. L. Traikov and Assoc. Prof. Margarita Raycheva.¹²

Statistical analysis

The results were analyzed with the Independent Samples T-test. The Mann-Whitney test was used for the Word List Recall Test due to the group's inhomogeneity. The level of

Table 1. Comparative statistical analysis of the groups of patients and controls (MMSE with Independent Sample T-test, Word ListRecall Test with Mann-Whitney Test)

Test	Group	Ν	Mean	Median	SD	Min	Max	р
MMSE	Controls	31	30	0	0	30	30	-0.001***
	Patients	103	29.05	1.22	1.20	27	30	<0.001***
Words List 1st Recall immediate recall	Controls	31	6.29	6.00	1.04	4.00	8.00	0 001444
	Patients	82	4.56	4.00	1.15	2.00	8.00	<0.001***
Words List 2nd Recall immediate recall	Controls	31	7.45	7.00	0.99	6.00	10.00	
	Patients	82	6.06	6.00	1.17	3.00	8.00	<0.001***
Words List Delayed Recall	Controls	31	7.03	7.00	0.87	6.00	10.00	
	Patients	82	6.20	6.00	1.44	4.00	10.00	0.001**
Word recognition	Controls	31	9.97	10.00	0.18	9.00	10.00	0.00011
	Patients	82	9.63	10.00	0.68	6.00	10.00	0.003**

statistical significance is expressed as a p-value between 0 and 1. A p-value of less than 0.05 (typically \leq 0.05) is statistically significant.

RESULTS

Comparative analysis between both groups of patients/controls showed statistical significance for MMSE (p < 0.001).

The results of the Word List Recall test were compared between the group of patients and the group of controls. The test was performed with two consequent immediate recalls, delayed recall, and word recognition. The results showed statistical significance for immediate and delayed recall, unconvincing recognition data. For immediate recall, the patient scores were 4.56 ± 1.15 and 6.06 ± 1.17 vs. 6.29 ± 1.04 and 7.45 ± 0.99 for controls, respectively. For delayed recall, the mean patient score was 6.20 ± 1.44 compared with 7.03 ± 0.87 , for recognition 9.63 ± 0.68 to 9.97 ± 0.18 (**Table 1**).

Beyond the statistical data is the cognitive profile of patients. Overall cognitive status assessed by MMSE indi-

cates the presence of 26 patients with an MMSE score between 25 and 28 points, which corresponds to mild cognitive impairment. MMSE subscale analysis finds deficits mainly in episodic and working memory when repeating three words, attention when calculating and when performing complex paper folding tasks. These results confirm the reported cognitive status of MMSE administration by Bawden et al.¹⁴ A positive correlation of MMSE and education (r = 0.412, p < 0.001) was found in the Pearson test correlation analysis (the better the education, the better the MMSE performance).

The Word List Recall test was administered to our patients in the following variant: Word List Recall - first attempt, immediate recall, Word List Recall - second attempt, immediate recall, Word List Recall - delayed recall after 30 minutes, Word List Recall - word recognition in a list that also contains unfamiliar words. Each of these tests gives us information about which memory processes are suffering: encoding, storage, and extraction. The information for coding appears from different stimuli: visual (picture, picture, and text), auditory (sound), semantic (meaning). The principle of encoding in short-term memory is an acoustic

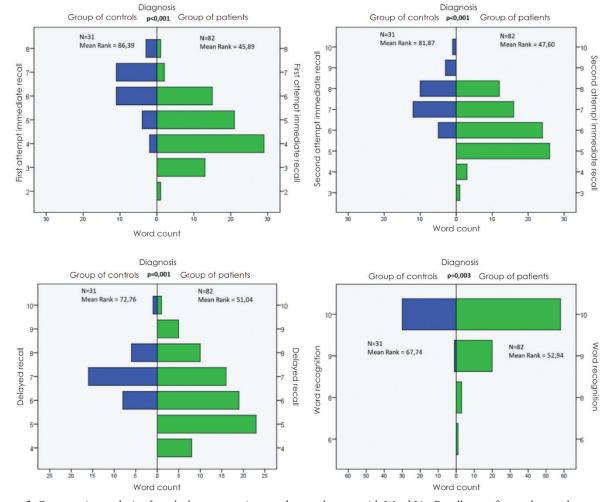


Figure 1. Comparative analysis of results between patients and control group with Word List Recall test – first and second attempt immediate recall, delayed recall, word recognition, presented with word count.

signal. When certain auditory information is presented, the patient retains it in the short-term memory by the verbal recall. The principle of encoding in long-term memory is predominantly with semantic meaning.

When we have to retrieve information, the distinction between long-term and short-term memory becomes especially clear. Short-term memory can hold 5 to 9 items (7 on the average). The information in the short-term memory remains around 0-30 seconds. Long-term memory is for life and the information is extracted by using associations.

Disorders of immediate recall indicate impaired attention, concentration and/or working memory, the information encoding suffers. They are a characteristic feature of frontal lobe disorders and are common in cerebrovascular disease. It is important to note that short-term memory and working memory are not straightforward concepts, working memory includes short-term memory, as well as other processes and mechanisms required to use shortterm memory.¹⁵ Engle defines working memory as the attention-related aspect of short-term memory.¹⁶ Working memory is also considered as that memory domain, which is affected by the executive functions.

Delayed recall provides information about the ability to recall information after a delayed period and is a hallmark of information storage and processing capacity. Recognition is the process of extracting already accumulated information from scattering elements. Recognition is a subcategory of declarative memory.

The results of the present study show the most pronounced disturbance of the immediate recall test, as well as disturbance of delayed recall to a lesser extent, minimal difference between patients and controls on recognition task was found (**Fig. 1**). When there is no recognition impairment in combination with impairment of immediate and delayed recall, it means that either the information has been encoded but not completely, or there is a deficiency in the retention and storage of the information. Another explanation is that the impairment of working memory is caused by a disorder of executive functioning.

The study found that the global cognitive functioning of patients with OSA and the memory function were impai-

red. Mostly short-term memory has been found affected in the studies of Lee et al.¹⁷, Findley et al.² and Borak et al.¹⁸, which confirm the data in this study but contradict the data of Grenèche et al.¹⁹ and Mathieu et al.²⁰, who do not find a deficiency in immediate recall in patients with severe OSA.

Factors relevant to the presence and severity of cognitive deficits of OSA are demographic characteristics, significance, comorbid conditions, and lifestyle. 70.9% of the 103 patients suffering from arterial hypertension (AH), 50.5% from hyperlipidemia, 27.2% from diabetes mellitus, 22.3% from ischemic heart disease.

Smoking, alcohol and psychoactive drug use have been considered in terms of lifestyle risk factors. Smoking is the most common harmful habit in patients (34% of our patients are smokers, 28.2% of patients are regular users of alcohol), data for the use of selective serotonin reuptake inhibitors are available for two patients, therefore, the role of this factor has not been analyzed in details.

Correlation between cognitive performance and some risk factors was sought by a comparative analysis of the results of cognitive tests of patients with or without a risk factor, AH, diabetes mellitus, dyslipidemia, the presence of bad habits. The results showed no statistical significance in the comparison of the groups for all the above mentioned factors. The comparative analysis between the groups of men and women shows no statistically significant differences in the average results of all cognitive methods. Obesity is a major factor relevant to the severity of cognitive changes in the study group. A statistically significant difference between the groups with and without obesity was found for the applied memory tests, except for the delayed recall and word recognition (Table 2). In the Baltimore Longitudinal Study, obesity was associated with impaired overall cognitive status, impaired memory, and impairment of verbal fluency tests.²¹ Obesity is a factor that has been found in previous studies to be associated with memory impairment.^{22,23} Type 2 diabetes mellitus is also associated with a delay in processing information and changes in working memory, changes in the verbal fluency tasks²⁴ but in our study, it was not confirmed.

In the course of the study, we hypothesized that the du-

Table 2. Comparative analysis of the results of cognitive tests with Independent Sample t-test between both groups – patients with bodymass index (BMI) <30 kg/m² and patients with BMI > 30 kg/m²

Test	BMI	Ν	Mean	SD	Min	Max	t	df
Word List Recall - immediate recall first attempt	≤30	36	5.72	6.00	1.41	3.00	8.00	<0.001***
	>30	77	4.71	5.00	1.21	2.00	8.00	
Words List Recall - immediate recall second attempt	≤30	36	6.94	7.00	1.37	3.00	10.00	0.002**
	>30	77	6.21	6.00	1.17	4.00	9.00	0.003**
Words List Recall - delayed recall	≤30	36	6.67	7.00	1.29	4.00	10.00	0.189****
	>30	77	6.31	6.00	1.39	4.00	10.00	
Word recognition	≤30	36	9.72	10.00	0.78	6.00	10.00	0.408****
	>30	77	9.73	10.00	0.50	8.00	10.00	

*p<0.05; **p<0.01; ***p<0.001 **** not statistically significant

Table 3. Comparative analysis between both groups (with symptoms duration >5 years and with symptoms duration<5 years) with Independent Sample Test

Test	Group symptoms duration	N	Mean	Me- dian	SD	Min	Max	p
Words List Recall - first attempt-immediate recall	>5 years	52	4.20	4.00	1.11	2.00	8.00	0.042*
	<5 years	30	4.93	5.00	1.18	3.00	7.00	
Words List Recall - second attempt, immediate recall	>5 years	52	5.98	6.00	1.04	4.00	8,00	0.031*
	<5 years	30	6.40	6.00	1.37	3.00	8,00	
Words List Recall - delayed recall	>5 years	52	5.94	6.00	1.39	4.00	10.00	0.028*
	<5 years	30	6.63	7.00	1.45	4.00	9.00	
Word recognition	>5 years	52	9.63	10.00	0.53	8.00	10.00	0.278****

*p<0.05; **p<0.01; ***p<0.001**** not statistically significant

ration of complaints is essential. The duration of exposure to hypoxia and sleep fragmentation is important for the severity of cognitive deficits. The results confirmed this theory showing that this factor is among the major severity factors (**Table 3**).

CONCLUSION

The study found that the global cognitive functioning of patients with OSA, as well as memory function, were impaired. The role of comorbidities is complex and far from clear. The main conclusion, after taking into consideration the role of risk factors, is that the severity of the impairment depends on the duration of the disease symptoms. The duration of exposure to the pathological changes leads to an accumulation of the effects and a more severe manifestation.

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Conflict of Interests

The authors declare that no competing interests exist.

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Общая когнитивная способность и оценка функций памяти при обструктивном апноэ во сне

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Резюме

Введение: Подозрения на наличие когнитивных проблем у пациентов с обструктивным апноэ во сне существуют с 1980-х годов. В многочисленных исследованиях были изучены различные когнитивные области. Подобного широкомасштабного исследования среди болгарского населения на данный момент не проводилось.

Цель: Целью данного исследования было оценить общее когнитивное функционирование и функции памяти у пациентов с обструктивным апноэ во сне и оценить потенциальное влияние сопутствующих заболеваний на когнитивные функции.

Материалы и методы: В исследовании изучался нейрокогнитивный профиль у 103 пациентов, у которых недавно было диагностировано обструктивное апноэ во сне и у 31 здорового человека в качестве контрольной группы. Был разработан список критериев включения и исключения. Дыхание во время сна было исследовано в обеих группах. Среди других используемых методов следует отметить: историю болезни пациентов, клиническое обследование, нейропсихологическую оценку, статистический анализ.

Результаты: Исследование показало, что общее когнитивное функционирование пациентов с обструктивным апноэ во сне и функция памяти были нарушены. Было обнаружено, что преимущественно кратковременная память была поражена. Только ожирение было определено в качестве основного фактора, связанного с тяжестью когнитивных изменений в исследуемой группе. Статистически значимая разница между группами с ожирением и без него была обнаружена при исследовании памяти не только в отношении замедленного припомнания слов, но и при распознавании слов. Длительность гипоксии и фрагментации сна важны для оценки тяжести когнитивных нарушений. Результаты подтвердили эту теорию и показали, что этот фактор является одним из основных факторов тяжести.

Заключение: Исследование показало, что общая когнитивная функция у пациентов с обструктивным апноэ во сне, а также функция памяти были нарушены. Роль сопутствующих заболеваний является комплексной и до сих пор не до конца выясненной.

Ключевые слова

общее когнитивное функционирование, память, обструктивное апноэ во сне