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Interaction between apolipoprotein E genotypes, excessive daytime sleepiness, and cognitive function in obstructive sleep apnea patients

Interação entre genótipos da apolipoproteína E, sonolência excessiva diurna e função cognitiva em pacientes com apneia obstrutiva do sono

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Abstract

Background Some studies show an association between the apolipoprotein E ε4 allele (ApoEε4) and obstructive sleep apnea syndrome (OSAS), and other studies, an association between ApoEε4 and excessive daytime sleepiness (EDS), but there are no data in the literature on the interaction between EDS, cognitive function, and ApoEε4 in patients with OSA.

Objective To examine the cognitive function of adults with and without EDS and with and without ApoEε4.

Methods A total of 21 male and female patients aged between 33 and 79 years, underwent a clinical interview, ApoE genotyping, neuropsychological evaluation, polysomnography, and the application of the Epworth Sleepiness Scale.

Results Excessive daytime sleepiness was associated with lower intelligence quotient (IQ; total performance) and worse immediate visual memory, regardless of the ApoE genotype. Patients carrying the ApoEε3/ε4 genotype had a worse performance in divided attention, constructional praxis, perceptual organization, and cognitive flexibility. A combination of the ε4 allele and EDS potentiates the negative effect on cognition, except for immediate visual memory. In this case, patients had a worse

Keywords
- Apolipoproteins E
- Sleep Apnea, Obstructive
- Disorders of Excessive Somnolence
- Cognitive Dysfunction

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performance in terms of processing speed, selective attention, and visuomotor coordination.

Conclusions Excessive daytime sleepiness and the ApoEε3/ε4 genotype are associated with worse cognitive performance in OSA patients. The combination of EDS and ε4 allele potentiates cognitive impairment.

Resumo

Antecedentes Alguns estudos mostram uma associação entre o alelo ε4 da apolipoproteina E (ApoEε4) e a síndrome da apneia obstrutiva do sono (SAOS), e outros, entre ApoEε4 e a sonolência excessiva diurna (SED), mas não há dados na literatura sobre a interação entre SED, função cognitiva e ApoEε4 em pacientes com SAOS.

Objetivo Avaliar a função cognitiva em adultos com SAOS com e sem SED e com e sem ApoEε4.

Métodos Ao todo, 21 pacientes, de 33 a 79 anos, homens e mulheres, foram avaliados clinicamente, e submetidos a genotipagem ApoE, avaliação neuropsicológica, polissonografia, e aplicação da Escala de Sonolência de Epworth.

Resultados A SED esteve associada com menor quociente de inteligência (QI; desempenho geral) e pior memória visual imediata, independentemente do genótipo ApoE. Pacientes com genótipo ApoEε3/ε4 apresentaram pior desempenho na atenção dividida, praxe construcional, organização perceptiva e flexibilidade cognitiva. A combinação do alelo ε4 com a SED potencializa esse efeito deletério na cognição, exceto na memória visual imediata. Nesse caso, os pacientes tiveram uma menor velocidade de processamento cognitivo, e piores atenção seletiva e coordenação visiomotora.

Conclusões A SED e o genótipo ApoEε3/ε4 estão associados a um pior desempenho cognitivo em pacientes com SAOS. A combinação de SED e do alelo ε4 potencializa esse efeito.

Palavras-chave

- Apolipoproteínas E
- Apneia Obstrutiva do Sono
- Distúrbios do Sono por Sonolência Excessiva
- Disfunção Cognitiva

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is associated with many etiological factors, including obesity, genetic inheritance, aging, craniofacial patterns, and sedative substances.[1,2] A sleep respiratory event is a partial or complete obstruction of the upper airway during sleep that is associated with negative intrathoracic pressure, oxygen desaturation, and increased respiratory effort, leading to arousal and sleep fragmentation.[3] Patients with OSAS present important functional impairment, including cognitive deficit and excessive daytime sleepiness (EDS).[4–6]

The apolipoprotein E (ApoE) gene is located in the long arm of chromosome 19 and presents 3 different alleles (ε2, ε3, and ε4) paired independently.[7] The ApoEε4 allele is associated with a cognitive deficit in otherwise normal individuals, age-related cognitive decline, Alzheimer disease, and cardiovascular disorders,[7–11] as well as OSAS in adults and children.[9–11] The ApoEε2 allele is considered neuroprotective and is associated with a lower age-related cognitive decline and a lesser predisposition to Alzheimer's disease.[12] The ApoEε3 allele is the most frequent in the general population, and it is considered neutral to cognitive performance.[13]

The association between OSAS and EDS is well established in the literature, and EDS is considered a predisposing factor for cognitive impairment.[14,15] Patients with OSAS and EDS present impairment in attention, alertness, memory, learning, and executive function.[16] Some OSAS patients do not present EDS and cognitive impairment, suggesting that other factors may be involved in the etiology of these disturbances.[17]

Some hypotheses have been proposed to explain how OSAS can affect cognitive performance independently from EDS. Several studies[18–20] have shown the direct association between cognitive dysfunction and OSAS. Intermittent hypoxemia can affect cognition due to neuronal damage in the cortex by increased oxidative stress.[21] Sleep fragmentation may also influence neuropsychological deficits.[14] The literature is not unanimous about the areas of cognition affected by OSAS. A meta-analysis by Wallace and Bucks[22] showed that OSAS is related to impaired episodic, verbal, and visuospatial memories. Other studies found that motor coordination, alertness, executive functions, and attention were the most affected functions.[23,24] In general, OSAS patients present long-term verbal memory and auditory working memory deficits, while OSAS patients with the ε4 allele have spatial working memory deficit.[25] A cohort study[26] found that OSAS

patients with the ε4 allele have impaired memory and executive functions. Another study[10] found that children with OSAS and the ε4 allele present more intense cognitive impairment.

A study by Caselli et al.[27] showed that EDS is associated with a decline in verbal memory in ApoEε4 homozygotes compared with heterozygotes. There are no data in the literature on the interaction between EDS, cognitive function, and ApoE4 in patients with OSAS. Considering that EDS could be related to the cognitive deficit in OSAS patients with different ApoE genotypes, we have proposed this study to evaluate this hypothesis.

METHODS

Patients and ethics

In total, 36 patients were consecutively recruited in the Sleep Medicine Clinic at Neuro-Sleep Center, Department of Neurology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil. All patients were submitted to baseline polysomnography (PSG). Patients with apnea-hypopnea index (AHI) > 15 were included. We did not select patients with other sleep disturbances and neurological, psychiatric, and clinical conditions that could affect cognitive performance and alertness at the discretion of the assisting physician. We did not select patients using substances that could affect cognitive function and alertness. Twelve patients were excluded because they did not meet the eligibility criteria or due to genotyping failure. The final sample was composed of 21 patients, 10 male and 11 female individuals, aged between 33 and 79 years. All patients signed a consent form. The present study was approved by the Research Ethics Committee of the Universidade Federal de São Paulo (#0494/16).

Procedure

The patients underwent a clinical interview, a physical examination, and the aplication of the Epworth Sleepiness Scale (ESS). Scores ≥ 10 on the ESS were indicative of EDS.[28–31] As aforementioned, all selected patients underwent baseline PSG. Blood samples were collected in ethylenediaminetetraacetic (EDTA) acid tubes and underwent polymerase chain reaction (PCR)-based genotyping for ApoE alleles. Genotypes ε3/ε3, ε2/ε4, and ε3/ε4 were identified in our sample. We compared patients (14) carrying the ε3/ε4 genotype with patients (7) carrying genotypes ε3/ε3 and ε2/ε4. Based on previous research,[13] in the latter group, ε2 was considered neuroprotective, ε3, neutral, and ε4, a predisposing allele.

We analyzed the neuropsychological parameters supposedly affected by OSAS.[32] The evaluation occurred in a controlled environment with adequate lighting and temperature. All neuropsychological tests were applied in a single session lasting approximately 2 hours and 30 minutes, with a 20-minute interval 90 minutes after the beginning of the evaluation. The evaluator was blinded to patient data on ESS, PSG, and ApoE. The cognitive tests applied were total intelligence quotient (IQ), verbal IQ, performance IQ, processing-speed index, symbol searching, Stroop color-word tests A, B, and C, the trail making test and the trail making test B, block design, matrix reasoning, Rey figure, forward digit span, forward and backward digit span, Rey auditory verbal learning test (RAVLT), and backward digit span.[33–37] The experimental procedures are summarized in ►**Figure 1**.

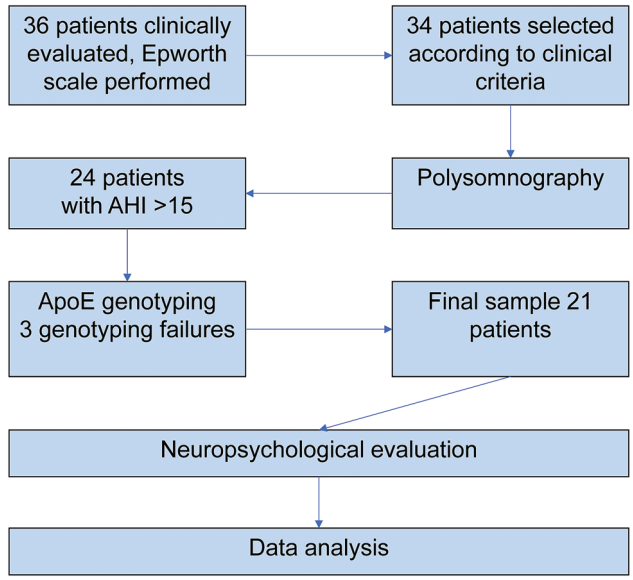

Figure 1 Experimental procedures.

Statistics

We calculated the means of the neuropsychological tests using gross scores for each cognitive function. The sample size was not calculated prior to the study. We normalized the results of different tests in terms of mean and standard deviation on a scale ranging from 0 to 100 and shown in a radar graph. The tests in which shorter times (in seconds) represented a better performance, the algebraic signal was inverted to be compared to the other neuropsychological parameters. We selected the Kruskal-Wallis test to compare the ε3/ε4 and non-ε3/ε4 groups for each cognitive function. The Chi-squared test was used to analyze the sociodemographic variables of gender, age, income, body mass index (BMI), and level of schooling. The Pearson correlation coefficient and Kruskal Wallis test were used to determine the influence of these variables in cognitive tests. We used the R (R Foundation for Statistical Computing, Vienna, Austria) statistical software for the statistical analysis and data management.[38–40]

RESULTS

A total of 4 (19%) patients had genotype ε2/ε4, 3 (14.3%) had genotype ε3/ε3, and 14 (66.7%), genotype ε3/ε4. We found no significant differences between groups concerning the sociodemographic parameters (►**Table 1**), and 61.9% of the patients had ESS scores ≥ 10, and 38.1%, < 10.

The distribution of patients in groups was as follows: EDS-ε3/ε4 (n = 8; 38.1%); EDS-non-ε3/ε4 (n = 5; 23.8%); non-EDS-

Table 1 Sociodemographic parameters of the study sample (n = 21)

	All genotypes		ApoE ε3/ε4		non-ApoE ε3/ε4	
	Mean	SD	Mean	SD	Mean	SD
Age	59.0	10.7	58.8	12.2	59.3	8.0
BMI	31.7	5.6	29.5	1.8	33.6	7.9
Gender	Frequency	Distribution	Frequency	Distribution	Frequency	Distribution
Male	10	47.6%	5	35.7%	5	71.4%
Female	11	52.4%	9	64.3%	2	28.6%
Schooling (years)	Frequency	Distribution	Frequency	Distribution	Frequency	Distribution
0-8	14	66,7%	10	71.4%	4	57.1%
9-12	4	19.0%	1	7.2%	3	42.9%
13-16	3	14.3%	3	21.4%	0	0%
Income group*	Frequency	Distribution	Frequency	Distribution	Frequency	Distribution
Low	12	57.1%	8	57.1%	4	57.1%
Medium	8	38.1%	5	35.7%	2	28.6%
High	1	4.8%	1	7.2%	1	14.3%

Abbreviations: ApoE, apolipoprotein E; BMI, Body Mass Index; SD, standard deviation.
Notes: *low: ≤ 3 monthly minimum wages; medium: 3 to 9 monthly minimum wages; high: > 9 monthly minimum wages.

ε3/ε4 (n = 6; 28.6%); and non-EDS-non-ε3/ε4 (n = 2; 9.5%). We assessed the differences among the groups by normalized data on a scale ranging from 0 to 100, as aforementioned (►**Table 2**). The EDS-ε3/ε4 group presented the worst cognitive performance, scoring below average in 9 categories (►**Figure 1**): total IQ (18.2 points below), performance IQ (24.6 points), processing-speed index (29.1 points), selective attention (21.8 points), constructional praxis (21.7 points), perceptual organization (37.1 points), visuomotor coordination (23.3 points), and cognitive flexibility (28.8 points) (►**Figure 2**). Polisomnography data are shown in ►**Table 3**.

Patients with genotype ε3/ε4, with and without EDS, presented a worse performance in divided attention (31.9 points), constructional praxis (21.7), perceptual organization (37.1), and cognitive flexibility (28.8). Those with EDS from both genotype groups presented a worse performance in total IQ (18.2), performance IQ (24.6), and immediate visual memory (19.4). Patients without EDS and genotypes other than ε3/ε4 presented a higher performance in total IQ (18.2), performance IQ (24.6), divided attention (31.1), perceptual organization (37.1), attention span (40.5), and cognitive flexibility (28.8 points) (►**Figure 2**).

DISCUSSION

Our results suggest that the ApoEε3/ε4 genotype in patients with moderate to severe sleep apnea and EDS is associated with impaired cognitive performance. The mechanisms through which the ε4 allele may affect cognition are not yet understood. According to some studies,[25] individuals with the ε4 allele have a higher incidence of cerebrovascular disease. Other studies[41] report that the presence of the ε4 allele is associated with lower metabolic rates in the posterior cingulate, inferior parietal cortex, and lateral temporal cortex. The ε4 allele is also related to a neurotoxic process that affects the mitochondria, cytoskeleton, and synaptogenesis, impairing cognitive function.[42]

In the sample of the present study, similarly to other studies, we found that EDS alone was associated with global cognitive impairment, which was evidenced by lower IQ scores, regardless of the association with the ε4 allele.[16]

A proposed mechanism for the etiology of EDS in OSAS is the fragmentation of sleep due to frequent arousals caused by respiratory effort, modifying sleep architecture.[6] Poor sleep quality is associated with memory disturbances. Sleep deprivation affects the hippocampus, compromising memory codification and retention and impairing its interaction with the visual cortex.[43] It can be related to low immediate visual memory performance in patients with EDS.

In the sample of the present study, when EDS and the ApoEε3/ε4 genotype occurred in the same patient, the cognitive disturbance was more intense than when they occurred isolatedly. A possible explanation is that genetic predisposition increases the vulnerability to the prejudicial effects of EDS on cognition.[44]

The main weakness of the present study is the small sample size, which limited the power of statistical analysis. We consider it a preliminary study that opens the path for future research in larger samples. Another limitation is the use of the ESS to assess EDS. Although the ESS is a validated and recognized instrument, it uses the patient's subjective perception, with the risk of false positives and false negatives.[31] Future studies with objective methods to assess sleepiness like the multiple sleep latency test and the maintenance of wakefulness test can lead to more accurate results.

In conclusion, the present study found that patients with OSAS, the ApoEε3/ε4 genotype, and EDS had impaired

Table 2 Neuropsychological data of the study sample

		EDS-ε3/ε4 (n = 8; 38.1%)		EDS-non-ε3/ε4 (n = 5; 23.8%)		Non-EDS-ε3/ε4 (n = 6; 28.6%)		Non-EDS-non-ε3/ε4 (n = 2; 9.5%)	
Cognitive function	**Tests**	**Score: mean ± SD**	**n/%***	**Score: mean ± SD)**	**n/%***	**Score: mean ± SD)**	**n/%***	**Score: mean ± SD)**	**n/%***
Selective attention	SyS	17.25 ± 7.36	1/12.5%	23.80 ± 5.80	0/0%	22.33 ± 5.80	0/0%	18.50 ± 0.70	0/0%
Divided attention	TMT	127.8 ± 68.30	3/37.5%	77.20 ± 48.44	2/40%	114.33 ± 58.89	3/50%	64.50 ± 33.94	0/0%
Constructional praxis	Cb	12.75 ± 16.15	7/87.5%	23.40 ± 13.14	3/60%	17.83 ± 15.31	4/66.7%	19.00 ± 4.24	1/50%
Perceptual organization	RF	7.00 ± 1.19	5/62.5%	6.60 ± 1.14	1/20%	6.16 ± 2.85	3/50%	9.00 ± 1.41	0/0%
Attention span	Dg	7.00 ± 1.19	0/0%	6.60 ± 1.14	0/0%	6.16 ± 2.85	2/33.3%	9.00 ± 1.41	0/0%
Immediate visual memory	RFR	13.43 ± 4.29	2/25%	13.40 ± 4.37	1/20%	17.66 ± 6.92	0/0%	16.75 ± 1.76	0/0%
Visuomotor coordination	Cd, Cb	24.12 ± 14.42	7/87.5%	34.60 ± 10.36	2/40%	30.66 ± 14.61	3/50%	30.50 ± 7.07	1/50%
Cognitive flexibility	TMT-B	201.37 ± 125.36	3/37.5%	109.60 ± 68.75	1/20%	183.83 ± 101.72	3/50%	95.00 ± 56.56	0/0%
Total IQ	Vc, Cb, Sm, MR	76.37 ± 17.57	7/87.5%	82.40 ± 13.90	3/60%	86.50 ± 20.40	3/50%	87.50 ± 7.77	1/50%
Verbal IQ	Sm, Vc	0.95 ± 0.55	6/75%	1.34 ± 0.75	4/80%	0.80 ± 0.31	3/50%	1.40 ± 0.56	1/50%
Execution IQ	Cb, MR,	81.62 ± 18.03	7/87.5%	81.60 ± 10.83	3/60%	89.16 ± 15.35	3/50%	89.00 ± 9.89	1/50%
Processing speed index	SyS, Cd	99.87 ± 8.27	1/12.5%	112.20 ± 8.25	0/0%	115.33 ± 16.02	0/0%	108.00 ± 11.31	0/0%

Abbreviations: EDS, excessive daytime sleepiness; Cb, cubes; Cd, Codes; Dg, Digits; IQ, intelligence quotient; MR, Matrix Reasoning; RF, Rey figure; RFR; Rey figure recall; SD, standard deviation; Sm, Similarities; SyS, Symbol Search; TMT, Trail Making test; TMT-B, Trail Making test B; Vc, Vocabulary.
Note: *n/% = % altered.

Table 3 Polysomnography data of the study sample

	All genotypes		ApoEε3/ ε4		non-ApoEε3/ε4	
	Mean	SD	Mean	SD	Mean	SD
TST (minutes)	346.8	53.0	357.0	58.3	326.3	35.4
WASO (minutes)	75.6	38.2	72.5	35.0	81.7	46.4
Sleep latency (minutes)	16.3	11.8	14.3	11.8	20.4	11.7
REM latency (minutes)	146.6	48.8	127.3	33.4	185.4	53.9
REM (%)	15.2	4.8	16.7	3.8	12.2	5.5
N1 (%)	16.1	8.8	15.5	9.0	17.4	9.0
N2 (%)	54.3	13.3	50.7	12.3	61.5	13.2
N3 (%)	17.2	15.7	17.9	9.7	15.8	24.8
AHI (events per hour)	34.1	15.9	32.6	16.1	37.2	16.3
Sat < 90% (%TST)	0.9	1.6	0.7	1.5	1.5	1.9
PLMI (events per hour)	3.9	13.9	5.6	16.9	0.6	1.6
Arousal index (events per hour)	32.8	16.2	32.5	15.9	33.5	18.0
ESS	9.0	5.2	8.0	5.8	10.9	3.5

Abbreviations: AHI, apnea-hypopnea index; ApoE, apolipoprotein E; ESS, Epworth Sleepiness Scale; N1, non-REM sleep stage 1; N2, non-REM sleep stage 2; N3, non-REM sleep stage 3; PLMI, periodic limb movement index; REM, rapid eye movement sleep; Sat, oxygen saturation; SD, standard deviation; TST, total sleep time; WASO, wake after sleep onset.

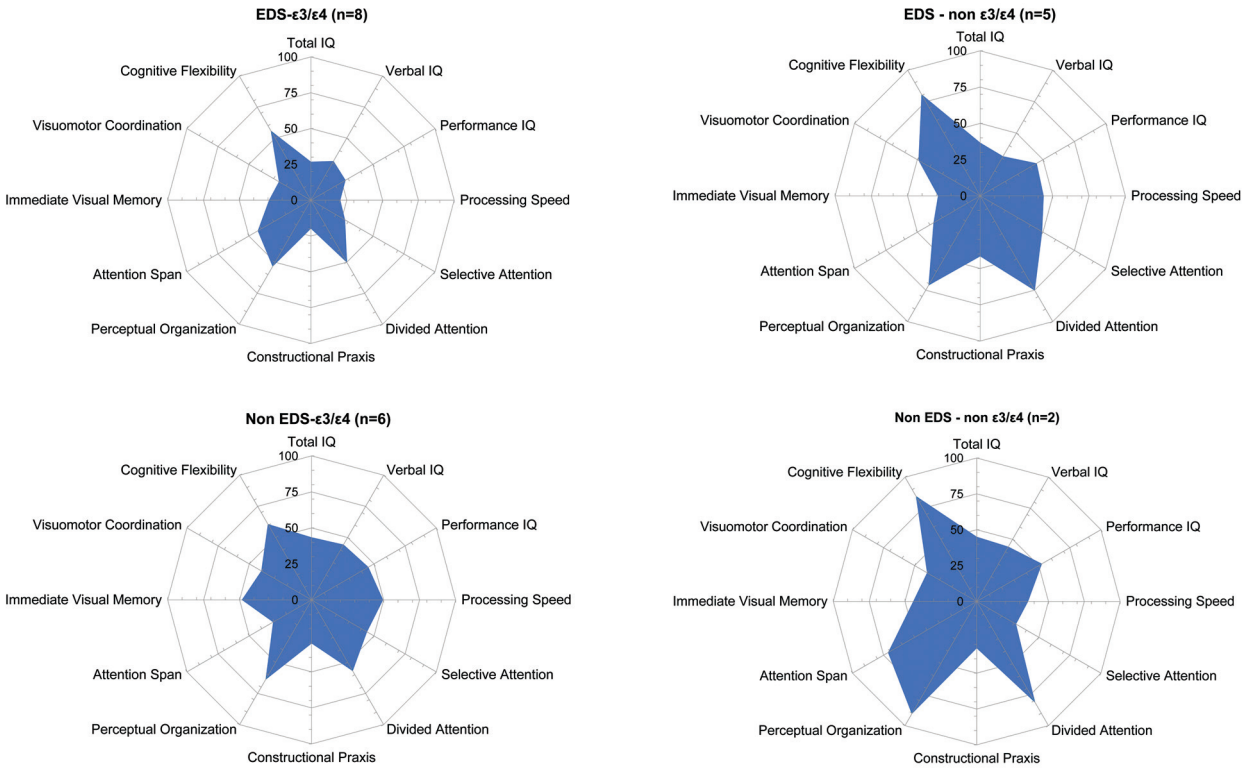

Figure 2 Differences in cognitive results among the groups (normalized data).

cognitive performance, and that a genetic factor may potentiate the harmful effect of EDS on cognition. Future investigations in this field can contribute to a better understanding and management of the clinical consequences of OSAS.

Authors' Contributions

FMB: hypothesis conception, data collection, analysis; WASM: hypothesis conception, data collection, article writing, analysis; JRH: hypothesis conception, statistics, analysis; GFP, LBCC: hypothesis conception, analysis, review.

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Conflict of Interest
The authors have no conflict of interests to declare.

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