ORIGINAL RESEARCH ARTICLE

Assessing Cognitive Impairment in Patients with Sleep-disordered Breathing Using Mini-mental State Score and Addenbrooke's Cognitive Examination—Revised

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Abstract

Aims and objectives: Obstructive sleep apnea (OSA), which is by far the most common form of sleep-disordered breathing, is associated with many other adverse health consequences including cognitive impairment. The screening methods for cognitive impairment in subjects with OSA are not well recognized. Mini-mental state score (MMSE) is the most widely used screening tool. This study was done to evaluate the utility of Addenbrooke's cognitive examination—revised (ACE-R) in comparison to MMSE.

Methodology and results: Thirty-six cases and controls [Epworth sleepiness score (ESS<10)] were recruited. They were administered using MMSE and ACE-R along with the online simulation test. The average age of both cases and controls was 49.2. Fourteen (58%) subjects had an MMSE score of less than 24, and 30 (81%) subjects had an ACE-R score of less than 82 thus qualifying for mild cognitive impairment (MCI). None of the controls had MCI. All subjects had severe OSA. The sleep parameters like apnea–hypopnea index (AHI), oxygen desaturation index (ODI), lowest saturation, and ESS had a negative correlation though not significant. Reaction time on the online simulator was increased in OSA as compared to controls.

Conclusion: The ACE-R can be used for screening for the presence of MCI in subjects with OSA and is a better screening tool than MMSE.

Keywords: Addenbrooke's cognitive examination—revised, Mild cognitive impairment, Mini-mental state score, Obstructive sleep apnea.

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Introduction

Sleep-disordered breathing is an umbrella term for several chronic conditions in which partial or complete cessation of breathing occurs many times throughout the night, resulting in daytime sleepiness or fatigue that interferes with a person's ability to function and reduces the quality of life. Obstructive sleep apnea (OSA), which is by far the most common form of sleep-disordered breathing, is associated with many other adverse health consequences, including an increased risk of death.[1]

Obstructive sleep apnea is[2,3] characterized by intermittent cessation of airflow, hypoxia, and repeated arousals, which increases the risk of various conditions, like hypertension, ischemic heart disease, stroke, and cognitive impairment. Of these, mild cognitive impairment (MCI) is the least commonly recognized comorbidity in subjects with OSA. Screening for MCI is not done routinely. The screening tools for MCI involve a large battery questionnaire that is hard-to-use, time-consuming, and intimidating not only to patients but also to their treating physicians who are not psychiatrists or psychologists. To add to the difficulty, it is not clear if the existing screening tools can be used in this population since studies indicate that only certain domains of MCI like attention/vigilance and visuospatial/constructional abilities are affected in individuals with OSA. Language ability and psychomotor function seem unaffected by OSA.

In view of these problems, an easy and effective method is needed to screen for cognitive deficits in OSA patients. In the absence of a specific screening tool for OSA subjects, we have to make do with the existing tools, of which mini-mental state examination (MMSE) is routinely used.

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The Addenbrooke's cognitive examination (ACE), incorporating MMSE in it, was developed to provide a brief test that is sensitive to the early stages of dementia. The naming component of the ACE had ceiling effects, and the visuospatial component was very limited. Hence some modifications were made to ACE. The expansion of the visuospatial domain in the revised version of ACE (ACE-R) increased the positive predictive value to 100% at the lower cutoff of 82 for a range of prevalence rates.

Hence ACE-R could be used to diagnose dementia in clinical settings, like OSA, where the visuospatial component is mainly affected.[4]

This study was undertaken with the aim of using the existing tool MMSE that has been studied previously in subjects with OSA and using another tool ACE-R, which has not been used in this population of OSA to look for the occurrence of MCI.

Materials and Methods

Participants consisted of 36 OSA patients and 36 age-matched controls. The study was conducted in the department of pulmonary medicine of a tertiary care teaching hospital over a period of 6 months. All subjects underwent a detailed medical history including any history of accidents, head injury, drug use, and physical examination.

Inclusion Criteria

Patients diagnosed with OSA on a full-night level 1 polysomnography aged between 18 and 59 years, who had not been initiated on treatment with a minimum education of high school level (to overcome test bias), were included. Thirty-six age-matched controls, who neither reported snoring nor suffered from daytime sleepiness [based on Epworth sleepiness scale (ESS) of less than 10], were selected from the hospital. The controls also were having a minimum of high school level of education.

Exclusion Criteria

Subjects and controls with known cognitive impairment, psychiatric illness, alcohol abuse, head injury, etc., were excluded.

The subjects and controls were evaluated for cognitive function by using ACE-R and MMSE along with the time-to-response test. The tests were done on the day patient came for a follow-up visit to collect the sleep study report. The ESS was employed to assess the daytime sleepiness.

Mini-mental State Examination

The MMSE questionnaire consists of several subscales: orientation, attention/calculation, immediate and short-term memory recall, and language and visuospatial skills. Cognitive deficit on the MMSE is defined as a score less than 24.[5]

Addenbrooke's Cognitive Examination—Revised

Addenbrooke's cognitive examination—revised is a 100-point test battery that looks at six cognitive domains. The ACE-R is a brief questionnaire that provides the evaluation of six cognitive domains (orientation, attention, memory, verbal fluency, and language and visuospatial ability).[4,6] It is useful for detecting dementia and MCI. The overall score is 100. A score of less than 82 is suggestive of MCI.

Time-to-response Tool

A Sleep and Health Education Program of Harvard Medical School has designed a Web tool (http://healthysleep.med.harvard.edu/need-sleep/whats-in-it-for-you/how-awake-are-you), with permission from Dr. Stuart F. Quan, consisting of a car driving simulation test to assess average time to response in subjects. This consists of a 5-minute car driving test on the Web, which gives a task to the subject of being a car driver on a highway on the computer screen that is automatically driven but with random objects appearing on the road for which the subject has to avoid crashing into. This requires the patient to be attentive and watch out for objects that will appear on the screen suddenly by pressing a button on the keyboard. The object appears randomly, and the patient is made to do this task of avoiding the objects for 5 minutes for which the average time to respond is calculated. Factors like the number of sleep hours the subject had the previous night and the number of hours he has been awake since then are also taken into consideration. The Web tool also calculates the average number of misses the subject makes.

This Web tool was used after taking permission from the designer of this Web tool at Harvard Medical School. All 72 subjects underwent this test at the same computer with the same Internet connection after two training sessions. This was done in the morning after the sleep study at about 10 a.m. for subjects and controls also at about the same time.

Epworth Sleepiness Scale

The ESS is a self-administered questionnaire that is used for the assessment of daytime sleepiness. It contains eight items involving eight daily-life scenarios, with each item being assessed on a 0–3 scale. The total scores of ESS range from 0–24. The cutoff point for excessive daytime sleepiness is set at >10.[7]

Polysomnographic Recordings

All patients received overnight polysomnography (Alice 5), including electroencephalography (C3/A2, C4/A1, O1/A2, O2/A1), electrooculography, submental electromyography, bilateral anterior tibialis electromyography, electrocardiography, nasal airflow measurement, monitoring of thoracoabdominal movements, oxygen saturation, snoring, and body position. Sleep stages and respiratory events were analyzed against the Sleep Medicine criteria (American Academy, 2007).[8]

The apnea was defined as complete stoppage of airflow for at least 10 seconds. The hypopnea was defined as a reduction in airflow by over 50% from baseline for at least 10 seconds with accompanying drop in arterial oxygen saturation of at least 4% and/or an electroencephalographic arousal. Scoring was carried out by an experienced technician.

Statistical Analyses

Descriptive statistics were used. The distribution of the data was analyzed by employing the Kolmogorov–Smirnov test. Data were presented as mean ± standard deviations for continuous variables with normal distribution.

Medians and averages were used for continuous variables without normal distribution and categorical variables. The Spearman's correlation analysis was performed to assess correlations between the parameters apnea–hypopnea index (AHI), oxygen desaturation index (ODI), and lowest oxygen saturation (L-SaO_2).

The study was approved by the institutional ethics committee of our hospital, and written informed consent was obtained from each participant.

Results

The average age of both cases and controls was 49.2. A total of 17 females and 55 males were recruited in the study.

None of the subjects had any history suggestive of cognitive dysfunction.

All the subjects were clinically diagnosed with OSA with a mean ESS in them of 11.4 (± 7.2). The sleep study showed severe OSA with AHI of 49.7 (± 27.2) events per hour, ODI of 42.9 (± 31), and mean lowest saturation of 85% (Table 1).

Controls had an ESS of 6 and below and had no sleep-related complaints.

Assessment of Cognitive Function

All the subjects and controls answered the MMSE and ACE-R.

Fourteen (58%) subjects had an MMSE score of less than 24, thus qualifying for MCI, whereas none of the controls had MMSE

less than 24. The mean MMSE was 26.3 (±3) in subjects and 28.3 (±1) in controls.

Thirty (81%) subjects had an ACE-R score of less than 82 and none of the controls qualified for MCI by ACE-R also.

None of the subjects in the study population qualified for moderate or severe cognitive impairment using either of the tools (Table 2).

The different cognitive domains as assessed by ACE-R were lower in subjects with OSA as compared with controls though the difference was not statistically significant (Table 3).

None of the sleep parameters, like AHI, ODI, ESS, or lowest saturation, had a strong correlation to the total MMSE or ACE-R score. The AHI had a stronger negative correlation to ACE-R score than MMSE (Corr Coeff— −0.17 vs −0.069).

Reaction Time

Subjects with OSA had a longer time to response on the online car driving simulation test (Sleep and Health Education Program of Harvard Medical School), 0.42 (± 0.08) vs 0.34 (± 0.03) though the difference was not significant ($p > 0.05$). The time to response did not correlate with ESS (Corr Coeff 0.022434), AHI (Corr Coeff 0.09), ODI (Corr Coeff 0.02), or lowest saturation (Corr Coeff 0.1).

Discussion

Neurocognitive impairment is known to occur in subjects with OSA but the exact prevalence of MCI in patients with OSA is not known. Since the cognitive profile is usually not due to an ongoing neurodegenerative process but due to chronic sleep fragmentation and intermittent hypoxemia that lead to attention, episodic memory, and executive dysfunctions even in younger adults. Hence this study was conducted to study the occurrence of MCI with the help of a new tool of ACE-R with 82 (the existing cutoff).

Table 1: Sleep characteristics in subjects with OSA

ESS (out of 24)	11.4 (± 11.4)
AHI	49.7 (± 27)
ODI	42.9 (± 31)
Lowest saturation	85%

Table 2: The total score on MMSE and ACE-R, in controls and subjects

	Subjects	*Controls*	*p value*
Age	49	47	
MMSE (out of 30)	26.3 (± 3)	28.3 (± 1)	0.0018
ACE-R (out of 100)	77 (± 11)	87.1 (± 1)	>0.05

Table 3: The scores of different domains of ACE-R among cases and controls

Cognitive domains	*Mean score in subjects*	*Mean score in controls*	*p value*
Attention (18)	12	15	>0.05
Memory (26)	18	24	>0.05
Fluency (14)	6	11	>0.05
Language (26)	16	18	>0.05
Visuospatial (16)	13	14	>0.05

The average age of our subjects was 49 years, which is much lower than the age at which we expect cognitive impairment to occur. Another Indian study also showed similar results.[9] Hence it is important to screen all subjects presenting to the sleep clinic for cognitive impairment irrespective of their age. None of our subjects had any other illness like diabetes or hypertension. The education level and age as confounding factors were considered in our subjects and controls.

All subjects had severe OSA. In other studies also, they had subjects with severe OSA[10] while others had all grades of severity.[11]

Global cognitive assessment using MMSE was significantly lower in cases as compared to controls and 58% subjects, and none of the controls had MCI (score <24). This is in tune with other studies that have used much sophisticated time-consuming tools, like Maze test or Stroop test.

Addenbrooke's cognitive examination—revised (ACE-R) was also lower in cases as compared to controls. (77 vs 87, >0.05) and was lower than the cutoff for MCI. The ACE-R score had a wider variation in subjects with OSA than in controls. Probably a larger sample would have brought out the difference better. As compared to MMSE, 81% of subjects qualified as MCI (score <82). This is the first time that this tool has been used to screen for MCI in OSA.

In our study, we found that with the higher AHI, ODI, and ESS and lower saturation, lower are the MMSE and ACE-R scores but this lacked statistical significance. The earlier studies also produced inconsistent results with regard to the cognitive effects of OSA. While in one study, it was negatively correlated[10] but others found no correlation between AHI and neurocognitive performance.[11,12] The methodology used to assess MCI was not uniform in other studies. Some studies have used simple questionnaires while others have used objective methods to look at MCI.

Similarly, time to respond also was longer, though not statistically significant in subjects than in controls. This is similar to the previous studies done before.[13] This would have a negative impact on the subject's ability to react to a given stimulus like during driving or operating heavy machinery and other tasks involving greater attention. This has been substantiated in previous studies.[9,14,15]

Conclusion and Summary

The ACE-R can be used to screen MCI in subjects with OSA. The whole screening of MMSE, ACE-R, and the online tool took 20 minutes. Hence it is important to screen all subjects attending the sleep clinic for cognitive impairment.

Suggestions

Specific questionnaires need to be designed along with psychomotor tests to identify early-onset decline in various areas like attention and time to response.[13] Further studies need to be done taking a larger population with the specific questionnaires designed and study the impact of treatment with continuous positive airway pressure on the cognitive function.

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