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Research Paper

Changes in Neurocognitive Architecture in Patients with Obstructive Sleep Apnea Treated with Continuous Positive Airway Pressure

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is a chronic, multisystem disorder that has a bidirectional relationship with several major neurological disorders, including Alzheimer's dementia. Treatment with Continuous Positive Airway Pressure (CPAP) offers some protection from the effects of OSA, although it is still unclear which populations should be targeted, for how long, and what the effects of treatment are on different organ systems. We investigated whether cognitive improvements can be achieved as early as one month into CPAP treatment in patients with OSA.
Methods: 55 patients (mean (SD) age: 47.6 (11.1) years) with newly diagnosed moderate–severe OSA (Oxygen Desaturation Index: 36.6 (25.2) events/hour; Epworth sleepiness score (ESS): 12.8 (4.9)) and 35 matched healthy volunteers were studied. All participants underwent neurocognitive testing, neuroimaging and polysomnography. Patients were randomized into parallel groups: CPAP with best supportive care (BSC), or BSC alone for one month, after which they were re-tested.
Findings: One month of CPAP with BSC resulted in a hypertrophic trend in the right thalamus [mean difference (%): 4.04, 95% CI: 1.47 to 6.61], which was absent in the BSC group [−2.29, 95% CI: −4.34 to −0.24]. Significant improvement was also recorded in ESS, in the CPAP plus BSC group, following treatment [mean difference (%): −27.97, 95% CI: −36.75 to −19.19 vs 2.46, 95% CI: −5.23 to 10.15; P = 0.012], correlated to neuroplastic changes in brainstem (r = −0.37; P = 0.05), and improvements in delayed logical memory scores [57.20, 95% CI: 42.94 to 71.46 vs 23.41, 95% CI: 17.17 to 29.65; P = 0.037].
Interpretation: One month of CPAP treatment can lead to adaptive alterations in the neurocognitive architecture that underlies the reduced sleepiness, and improved verbal episodic memory in patients with OSA. We propose that partial neural recovery occurs during short periods of treatment with CPAP.

1. Introduction

Obstructive sleep apnea (OSA) is a debilitating, chronic multisystem sleep disorder that arises from recurrent partial or complete pharyngeal obstruction during sleep (Lévy et al., 2015; Malhotra et al., 2015). It has been proposed to have an important, if not fully understood, bidirectional relationship with several major neurological disorders (Lévy et al., 2015; Rosenzweig et al., 2015; Rosenzweig et al., 2014). A close association of OSA with early onset of cognitive decline, by as much as a decade, has been reported, whilst a growing body of clinical and animal work advocates that OSA should be recognized as one of the rare modifiable risks for Alzheimer's dementia (Rosenzweig et al., 2015; Osorio et al., 2015; Yaffe et al., 2014). In addition, treatment with Continuous Positive Airway Pressure (CPAP), the main treatment for OSA, has been also variably shown to halt the onset, decelerate the progression, or offer a better prognosis in patients with co-morbid dementia,

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epilepsy and stroke (Osorio et al., 2015; Yaffe et al., 2014; Campos-Rodriguez et al., 2014; Pornsriniyom et al., 2014; McMillan et al., 2015).

Numerous clinical studies over the years have demonstrated changes in the central nervous system (CNS) of patients with OSA, including altered resting cerebral blood flow pattern (Baril et al., 2015) with hypoperfusion during the awake states (Joo et al., 2007), changes in the electroencephalogram (EEG) and aberrant cortical excitability (Morisson et al., 1998, 2001; Dingli et al., 2002) and changes in both white and gray matter (Zimmerman and Aloia, 2006; Torelli et al., 2011; Kumar et al., 2014; Morrell and Glasser, 2011; Macey et al., 2008). These studies have largely also suggested a putative neurocircuitry fingerprint at which core lies the disconnection of the frontal regions (O'Donoghue et al., 2012) and the disruption of the (cerebello)-thalamocortical oscillator with involvement of the hippocampal formation (Rosenzweig et al., 2013a, 2014; Torelli et al., 2011; Yaouhi et al., 2009).

The additive impact of progressive changes in sleep quality and structure, changes in cerebral blood flow, neurovascular and neurotransmitters, plus the cellular redox status are all likely to contribute to the cognitive deficits reported in up to one out of four newly diagnosed OSA patients (Rosenzweig et al., 2015; Lavie, 2015; Antonelli Incalzi et al., 2004). Despite concerted efforts, OSA remains widely underdiagnosed in the general population, with its prevalence predicted to increase sharply over the coming years due to the epidemics of aging and obesity (Lévy et al., 2015; Heinzer et al., 2015). The important questions of what, who and when to treat, are far from clear (Rosenzweig et al., 2015; Djonlagic et al., 2015; Dalmases et al., 2015). Persistent deficits, even after prolonged treatment with CPAP in some patients, suggest that early detection of the central nervous system (CNS) sequelae in OSA could be crucial (Rosenzweig et al., 2015; Castronovo et al., 2014; Kylstra et al., 2013).

In a recent study of patients with OSA, augmentation of subjective experience, attention and vigilance has been demonstrated after only one night of CPAP (Djonlagic et al., 2015). However, no appreciative impact on procedural memory consolidation was noted, suggesting differential impact on brain structures underlying these processes (Djonlagic et al., 2015). On the other hand, in a seminal study, three months of CPAP treatment led to a significant recovery of cognitive and morphometric deficits (Canessa et al., 2011). Taken together, empirical clinical experience and early research findings suggest that subjective memory improvements are reported as early as one month following the commencement of CPAP treatment (McMillan et al., 2015). In the present study, we set out to investigate this time frame, testing the hypothesis that one month of CPAP treatment would lead to cognitive improvements, and that any changes would be associated with neuroplastic changes in patients with OSA.

2. Methods

2.1. Participants And Design

Patients with newly diagnosed OSA (18–65 years old) were recruited from Royal Brompton and Harefield Hospitals' sleep clinics. Inclusion criterion was an apnea/hypopnea index (AHI) >10 events/h (McMillan et al., 2014). Apneas were defined as >80% drop in airflow for 10 s. Hypopneas were defined as >50% reduction in airflow from baseline with a >4% dip in saturation, or an arousal from sleep (Berry et al., 2012a, 2012b; Rosenzweig et al., 2013b). Exclusion criteria were a history of respiratory, cerebrovascular and/or ischemic heart disease, diabetes mellitus, neuropsychiatric or neurological disorder, alcohol, drug abuse, or psychoactive medications.

The same exclusion criteria were used for healthy controls (age- and education-matched) recruited from a database of healthy volunteers. Those with a history of sleep problems on questionnaires, or evidence of OSA on pulse-oximetry (ODI > 5 events/h) were excluded.

All enrolled patients were randomly allocated [stratified by age, OSA severity (oxygen desaturation index (ODI) & AHI) and years of education], by an independent study coordinator, to receive CPAP with best supportive care (BSC), or BSC alone, for one month and then re-assessed (Fig. 1).

The study was part of an ongoing research to investigate the impact of OSA on the brain and was approved by the UK central research ethics committee (10/H0706/51). All patients gave written informed consent.

2.2. Intervention

CPAP treatment was initiated using standard clinical practice at each center (ResMed S9; with humidification as required).

BSC comprised of advice on minimizing daytime sleepiness through sleep hygiene, naps, caffeine, exercise and weight loss as appropriate to each patient. Both groups were provided with BSC and asked to continue with their usual medical care during the trial.

2.3. Assessments

Structured assessments were performed at baseline (patients and controls) and a follow-up after one month (patients only). In addition, all patients received a telephone call at 1 week to record symptoms, side-effects, and to optimize CPAP adherence. All OSA patients completed an inpatient polysomnography (SOMNOscreen PSG, S-Med, UK) prior to CPAP initiation. Domiciliary overnight pulse-oximetry (Konica Minolta Inc.,) was performed at one month. Treatment compliance was measured objectively by download of the CPAP smart card during the one-month visit.

2.4. Cognitive Test Battery

Cognitive function of all participants was assessed using a battery of tests comprising the Addenbrooke's Cognitive Examination-Revised (ACE-R) (Mioshi et al., 2006; Graham et al., 2004), Trail Making Test A and B (Reitan, 1979) (TMA, TMB), Logical Memory (LM) Test: immediate and delayed LM with alternate stories used at baseline and follow up, subtests from the Wechsler Memory Scales (Wechsler, 1987), Digit Span Test: forward (DSF) and backward (DSB) (Wechsler, 1987), and Spatial Span subtest forward (SSF) and backward (SSB) (the visual–spatial version of Digit Span) (Wechsler, 1997). The tests used were chosen to target cognitive domains that have been previously shown to be affected by OSA, by our group and other groups (Rosenzweig et al., 2015; Twigg et al., 2010).

ACE-R is a brief battery that provides evaluation of six cognitive domains (orientation, attention, memory, verbal fluency, language and visuospatial ability) (Mioshi et al., 2006). It is useful for detecting dementia and mild cognitive impairment, and it is able to distinguish between patients with progressive degenerative disorders and those with affective disorders (Dudas et al., 2005). The total score is 100, higher scores indicate better cognitive functioning, each domain has individual scores and there are age and education dependent norms for the total score as well as for the individual domains (Mioshi et al., 2006). The subscores for the domain of verbal fluency (ACE-R verbal fluency) were used in this study to asses both executive and language abilities (Shao et al., 2014).

The TMT consists of two parts, A and B; it is one of the most widely used neuropsychological tests that provides information on visual conceptual and visuomotor tracking, motor speed, attention and executive functions (Reitan, 1979). It is a timed test and the score represents the amount of time required to complete the task (Reitan, 1979). Performance decreases with increasing age and lower levels of education although normative data is available (Tombaugh, 2004).

Wechsler Adult Intelligence Scale, third edition (WAIS-III) (Wechsler, 1997) is a commonly used commercially available validated assessment of cognitive function. The LM, DSF, DSB, SSF and SSB tests