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IMPACT OF OBSTRUCTIVE SLEEP APNEA IN THE EVOLUTION OF ALZHEIMER DISEASE. ROLE OF HYPOXIA AND SLEEP FRAGMENTATION

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1. Abstract

Introduction: Alzheimer's disease (AD) is the most frequent cause of dementia worldwide and it is characterized by progressive deterioration in cognition, function and behaviour, which places a considerable burden on society.

Between 25-40% of patients with mild and moderate AD have sleep problems and obstructive sleep apnoea (OSA) is present in up to 50%. There is a bidirectional relationship between sleep disturbance and AD. Sleep fragmentation increase expression of Aβ 42. On the other hand, hypoxia facilitates the pathogenesis of AD through multiple mechanisms such as increasing amyloid beta (Aβ) generation, stimulating the hyperphosphorylation of tau and impairing blood-brain barrier function. Both sleep fragmentation and intermittent hypoxia are present in OSA. However, no data are available about the impact of OSA on the progression of the disease in patients with symptomatic AD and the relative importance of sleep fragmentation and/or hypoxia in this group of patients.

Objectives: Our hypothesis is that OSA worsens the cognitive and behavioural progression of patients with AD. The mouse model is excellent for studying the pathophysiological pathways of disease progression under conditions of intermittent hypoxia and sleep fragmentation. The objectives of the study were: To evaluate the cognitive and behavioural progression in patients with mild AD with and without OSA. To identify biomarkers that help evaluate the progression of AD. To establish a mouse model with intermittent hypoxia (IH) and sleep fragmentation (SF). To characterize the cognitive and behavioural performance of the mouse model in different periods of time.

2. Results

The cohort included 128 patients with a median [IQR] age of 75.0 [72.0;79.2] years and 57.8% were women. OSA was diagnosed in 116 subjects (90.6%). The distribution of mild, moderate and severe OSA was 29 (22.7%), 37 (28.9%) and 50 (39.1%) respectively. The cohort showed normal values of daytime sleepiness (median EES score 5 [3;8]), while nocturia (89.1%) and snoring (71.1%) were the most common symptoms.

Participants with severe OSA included a higher proportion of older men, and were associated with snoring and sedentariness. No significant differences in cognitive assessment were found between patients with and without severe OSA in any of the domains. The prevalence of APOE ε4 was not significantly different between patients with and without severe OSA.

Despite this high prevalence of OSAS, it has been observed that the clinical screening scales for it such as the STOP-BANG and the Berlin scale are not useful for the detecting it, reinforcing the need to create specific scales for this type of population. In the mouse model, male C57BL/6J mice were exposed to either IH or room air (RA) for 3-240 days, and then half were randomly selected and allowed to recover in normoxic conditions for the same duration of the previous exposure. A novel object recognition test (NOR) was performed. NOR performance was stable over time in RA. IH induced significant reductions in recognition index that progressed over the first 45 days and stabilized thereafter. Normoxic recovery of recognition index was essentially complete and indistinguishable from RA in mice exposed to shorter IH exposures (<90 days). However, significant residual deficits emerged after normoxic recovery following prolonged IH exposures ($p<0.01$). In addition, gradual attenuation of the magnitude of recovery in recognition index occurred with increasingly longer IH exposures (MANOVA $p<0.0001$). IH during the resting period reduces NOR performance time-dependently. Reversal of NOR performance deficits is unlikely after prolonged IH duration. These findings suggest that early recognition of sleep apnoea and effective treatment are critical for restoration of the adverse cognitive effects of the disease. Sleep fragmentation in murine models was shown to increase the expression of phosphorylated tau in ser396 without altering amyloid levels.

We expanded on our work in exosomes. To this effect, exosomes were isolated from plasma from OSA patients before (n=20; mean age 56 years, 10 women; BMI: 29.4) and after 3 months CPAP treatment (n=20; adherence >85%, >6 hrs/night), 10 age, gender, AHI, and BMI matched patients who decided not to use CPAP, and matched controls without OSA (n=12). Isolated exosomes were added to an in vitro blood-brain barrier (BBB) system that we have recently described in children (Khalyfa A, Gozal D, Kheirandish-Gozal L. Plasma Exosomes Disrupt Blood Brain Barrier in Children with OSA and Neurocognitive Deficits. Am J Respir Crit Care Med. 2017 Oct 20. doi: 10.1164/rccm.201708-1636LE. [Epub ahead of print] PubMed PMID: 29053009) and

the changes in electric current field resistance (TEER) were measured over time, revealing significant disruption of the BBB only in the group with OSA when compared to the control group ($p<0.001$). no changes in BBM disruption emerged in the untreated OSA group, while significant improvements occurred after CPAP treatment ($p<0.001$). Furthermore, we exposed primary cultured neurons to exosomes from patients with untreated OSA and matched controls without OSA and evaluated the expression of phosphorylated tau at ser396 (clone EPR2731, Abcam) using western blots (see figure below).

Conclusions: There was a high prevalence of OSAS in patients with mild-moderate AD. OSAS was not associated with somnolence or worse cognitive function. APOE ε4 was not related to the presence or severity of OSAS. Further longitudinal studies will be required to evaluate whether OSAS affects cognitive evolution in patients with AD. In animal models and cell cultures, both IH and sleep fragmentation have been shown to alter the cognitive performance of murines and increase the expression of hyperphosphorylated tau.