Sohag University Sohag Medical Journal Faculty of Medicine

Obstructive Sleep Apnea and Alzheimer's Disease: A Two-way Street.

Enas Khalifa Ahmed Abuzied[1], Manar hamza sayed[2], Ahmed Ezzat Amin[2], Sara Kasem Abdelaal[3], Rofaida M. Magdy[4], Ayman abdelmotelb[5], Doaa Mohamed gad[6], Ebtisam Mohammed Gad[1].

1. Department of Chest diseases and Tuberculosis, Faculty of Medicine, Sohag University.
2. Department of Neuropsychiatry, Faculty of Medicine, Sohag University.
3. Department of Internal Medicine, Faculty of Medicine, Sohag University.
4. Department of Pediatrics, Metabolic and Genetic Unit, Faculty of Medicine, Sohag University.
5. Department of Cardiothoracic Surgery, Faculty of Medicine, Sohag University.
6. Department of Otorhinolaryngology, Faculty of Medicine, Sohag University.

Abstract

Background:- Obstructive sleep apnea syndrome (OSAS) and Alzheimer's disease (AD) are really widespread chronic diseases with increasing impact on the elderly group in our society. Nowadays, many causes of obstructive sleep apnea are well identified, while Alzheimer's disease related mechanism are still not recognized, challenging the arrival to an actual treatment. Cognitive impairment is a clinical recognized consequence of obstructive sleep apnea, which is a result of intermittent hypoxia, disruptions of sleep architecture, oxidative stress, hemodynamic and transthoracic pressure changes, all of these factors increase the Alzheimer's disease risk in patients with obstructive sleep apnea. On the other hand, Alzheimer's disease can aid the emergence of obstructive sleep apnea by revealing serotonin and acetylcholine deficit; which are vital neurotransmitters for upper airway patency.

Purpose of this review article: - it aims to focus on the pathophysiologic relationships between Alzheimer's disease and obstructive sleep apnea and the role of early detection and treatment of obstructive sleep apnea on the evolution of Alzheimer's disease.

Conclusion: - Obstructive sleep apnea and Alzheimer's disease are a Two-way Street; having a bidirectional effect on each other's pathogenesis. Alzheimer's disease can aid the emergence of obstructive sleep apnea which itself facilitates neuronal apoptosis and neurodegeneration. It is a necessary for neurologist to screen obstructive sleep apnea in any Alzheimer's disease patient and vice versa.

Keywords: Alzheimer's disease, Obstructive sleep apnea , Pathophysiology.

DOI:10.21608/SMJ.2023.183672.1360

Introduction

Alzheimer's disease (AD) and Obstructive sleep apnea (OSA) are both extremely widespread chronic diseases with a significant impact on the world health.(1)

Obstructive sleep apnea is the most common sleep-related breathing disorderrs, accounting approximately 85% of the cases, whereas sleep apnea of central

cause is less common.[2] OSA is characterized by repetitive events of upper airway obstruction during sleep, leading to either partial or total air flow limitation, inspite of constant respiratory muscles effort.[3]

OSA is frequently associated with numerous comorbidities. All features of metabolic syndrome, specifically hypertension, diabetes, obesity and dyslipidemia have been accompanied with OSA. In addition to its known direct consequence on cognitive performance, collecting evidence is nowadays supporting the role of OSA in the pathogenesis of dementias.[4] OSA severity is assessed by apnea-hypopnea index (AHI), which represents the total apnea and hypopnea episodes per hour of sleep. AHI of people with mild OSA equals 5–14 events/hour, that of moderate OSA values 15–29 events/hour while that of severe OSA values ≥30 events/hour.[5]

Apneas are defined as cessation in respiratory airflow greater than 90% for a duration greater than 10 seconds, while hypopneas, are defined as reductions in inspiratory airflow of greater than 30% for duration >10 seconds, accompanied by arousal or reduction in oxygen saturation of at least 3%. The difference between CSA and OSA is that a blocked airway isn't what prevents a person from breathing—people with CSA experience respiratory distress as the brain fails to properly signal the muscles that control breathing function.[6]

The first line of treatment in most OSA patients is the continuous positive airway pressure (CPAP), that decreases the AHI professionally and regulates the oxyhemoglobin saturation and the frequency of arousals/ awakenings by returning the upper airway patency during sleep.[7]

Alzheimer's disease is one of the 21st century's challenges. It is one of the systemic neurodegenerative disorders of unidentified etiology. It is the most common type of dementia, representing greater than 70% of dementia cases. The recognized background which explains the individual tendency for AD developpment is the combination of environmental and genetic factors. It is usually associated with cognitive deficits especially in the elderly.[8]

The origin of neurodegeneration differs with various neurological diseases, abnormal accumulation of specific proteins due to failure of the cells to fold them in their unique shape, resulting in the formation of inclusion bodies or fibrillar aggregates, appears to be the most common pathophysiological mechanism among these disorders.[9]AD is classically characterized by progressive decline in the memory and other irreversible deficits in the cognition in addition to the neuronal loss and the cerebral atrophy.[10]

Relationship between AD and OSA

The relationship between AD and OSAS has been recently suggested to be bidirectional,as being illustrated in figure[1], in which one disorder affecting the other and vice-versa.[11]AD patients have the tendency to present with OSA, 5 times higher compared to age matched controls, and nearly 50% of the patients with AD develop OSA after their primary diagnosis. On the contrary, OSA may accelerate the age of onset of AD or encourage the worsening of existing AD.[12]

1- Aging in OSA and AD

Neurodegenerative disorders usually affect the elderly i.e. who are also susceptible to upper airway obstruction. Nevertheless, the high proportion of OSAS in AD patients (53.9%) suggests that certain mechanisms of the neurodegene-

rative pathway are related to the normal aging-changes that affect the respiratory system to promote the OSA development in the elderly group.[11] The phenomenon of the lower ventilatory reaction to both hypoxia and hypercapnia with aging seems to be related to:-

- The reduction of the chemoreceptors sensitivity to changes in pH, O2 and CO2.
- The changes in the structure of the respiratory system with aging; narrowing the lumen with more soft tissue surrounding it, and reduction in the negative pressure reflex.[13]

1- Genetics in OSA and AD

Genetic predisposition is another fact of combination between OSA and AD. Carriers of the apolipoprotein Eε4 (APOEε4) gene have greater tendency to develop both OSA and AD, and the detection of APOEε4+ gene in OSA patents was associated with worse impact on the memory and the executive functions compared to those who carrying APOEε4. [14]

2- OSA as a risk factor for AD

OSA is essentially accompanied with sleep pattern disruptions, oxidative stress, intermittent hypoxia, cardiovascular comorbidities.

Intermittent hypoxia, as a consequence of OSA participates in the emergence of AD by many mechanisms. Firstly, intermittent hypoxia stimulates the expression of genes associated with cellular apoptosis and inflammation.[15] Secondly, intermittent hypoxia accelerates the accumulation of amyloid precursor protein (APP) in the CNS by stimulating BACE1 (β-site amyloid precursor protein cleaving enzyme) activation.[16] Thirdly, hypoxia increases the activation of pro-inflammatory pathways and the production of reactive oxygen species involving in neuronal apoptosis.[17]

Reduced amyloid clearance and its accumulation in brain cells, which enhances the developing of AD, is considered as a different pathway by which OSA could increase the risk of AD by the following mechanisms: -

- **Mechanical changes in OSA** :- During the apneic episodes of OSA, the breathing effort against the collapsed airways (Mueller maneuver) is accompanied with rising in the intrathoracic and intracranial pressures and disturbance in hemodynamic circulation which delays brain metabolites clearance through the glymphatic system, resulting in increased Aβ42 accumulation in brain interstitial fluid (ISF).[18]

- **Brain changes in OSA (cerebral edema):** The intermittent hypoxia associated with OSA causes cerebral edema by cerebrospinal fluid- interstitial fluid (CSF-ISF) exchange impairment. Increased volume and thickness of certain parts of the cortex was observed in cases with severe OSA. These changes were noticed to reverse after CPAP treatment for six months, suggesting the occurrence of brain edema in cases of OSA.[19]

3- AD as a risk factor for OSA.

Impairment in cholinergic transmission that found in AD can promote the developing of apnea, because cholinergic activity has an impact on the upper airway muscle tone. Donepezil is one of central acetylcholinesterase inhibitors which lowers the AHI in AD patients associated with OSA. Nevertheless, the evidence to suggest the use of this medication in treatment of OSA in AD patients is insufficient.[20] Also structures of gray

matter and white matters that control motor response are affected in patients with AD either by neuronal loss or accumulating pathology and that possibly promoting their susceptibility for developing OSA.(21)

Use of CPAP in AD patients

Considering that OSA is a probably treatable disease, its early recognition and interference could have a helpful effect on slowing down the progression of dementia in AD patients.(22) CPAP therapy has been wished to be an efficient mean of restoring the quality of sleep and cognitive function in AD patients. Early CPAP handling should be considered in AD patients when OSAS is co-existing.(23)

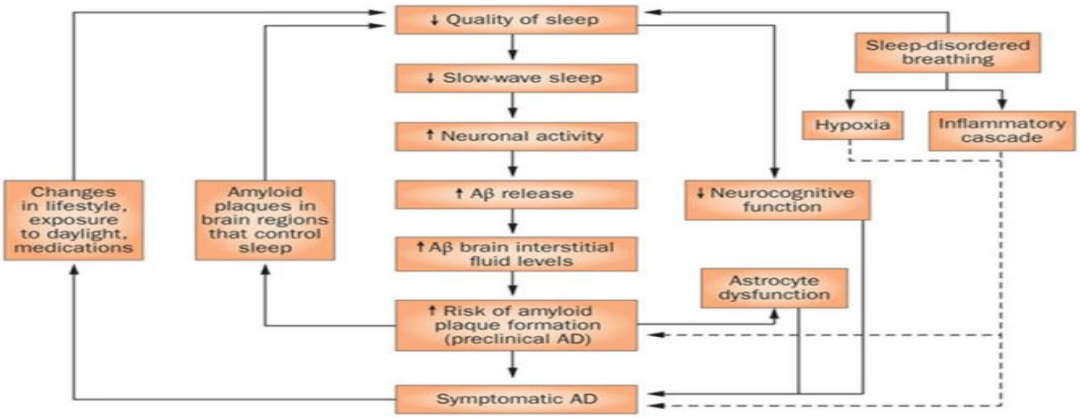

Figure (1) Obstructive sleep apnea and Alzheimer's disease relationship. (24)

***The challenge for the coming studies is* :**

Better assessment of the involved mechanisms either being genetic or environmental factors and development of knowledge on this bidirectional relationship should be continued.

Conclusions

Obstructive sleep apnea and Alzheimer's diseases are a two-way street; having a bidirectional effect on each other's pathogenesis. AD can aid the emergence of OSA, and OSA also promotes neuronal apoptosis and neurodegeneration. Since no restorative treatment for AD is now available, early diagnosis of OSA in AD patient can help in delaying progression of the disease.

References

1. Lipsman, N., Meng, Y., Bethune, A. J., et al. Blood–brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. *Nature communications. 2018;9* (1), 1-8.
2. Morgenthaler, T. I., Kagramanov, V., Hanak, V., et al. Complex sleep apnea syndrome: is it a unique clinical syndrome? Sleep. 2016;29(9), 1203-1209.
3. Eastwood, P. R., Malhotra, A., Palmer, L. J., et al. Obstructive sleep apnoea: from pathogenesis to treatment: current controversies and future directions. 2010; *Respirology*, *15*(4), 587-595.
3. Andrade, A. G., Bubu, O. M., Varga, A. W., et al. The relationship between obstructive sleep apnea and Alzheimer's disease. *Journal of Alzheimer's Disease. 2018; 64*(s1), S255-S270.

4. Ferini-Strambi, L., Lombardi, G. E., Marelli, S., et al. Neurological deficits in obstructive sleep apnea. *Current treatment options in neurology. 2017; 19*(4), 1-13.

6. Berry, R. B., Budhiraja, R., Gottlieb, D. J., et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events: deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. *Journal of clinical sleep medicine.2012; 8*(5), 597-619.

7. Can, O. What is obstructive sleep apnea in adults? *Am J Respir Crit Care Med. 2017;196*, P1-P2.

8. Frost, G. R., & Li, Y.-M. The role of astrocytes in amyloid production and Alzheimer's disease. *Open biology. 2017; 7*(12), 170228.

9. Jellinger, K. A. Interaction between pathogenic proteins in neurodegenerative disorders. *Journal of cellular and molecular medicine. 2012; 16*(6), 1166-1183.

10. Malhotra, R. K. Neurodegenerative disorders and sleep. *Sleep medicine clinics. 2018; 13*(1), 63-70.

11. Irwin, M. R., & Vitiello, M. V. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. *The Lancet Neurology. 2019; 18*(3), 296-306.

12. Emamian, F., Khazaie, H., Tahmasian, M., et al. The association between obstructive sleep apnea and Alzheimer's disease: a meta-analysis perspective. *Frontiers in aging neuroscience. 2016; 8*, 78.

13. Lalley, P. M. The aging respiratory system—pulmonary structure, function and neural control. *Respiratory physiology & neurobiology. 2013;187*(3), 199-210.

14. Nikodemova, M., Finn, L., Mignot, E., et al. Association of sleep disordered breathing and cognitive deficit in APOE ε4 carriers. *Sleep. 2013; 36*(6), 873-880.

15. Vetrugno, R., Provini, F., Cortelli, P., et al. Sleep disorders in multiple system atrophy: a correlative video-polysomnographic study. *Sleep medicine. 2004; 5*(1), 21-30.

16. Daulatzai, M. A. Death by a thousand cuts in Alzheimer's disease: hypoxia—the prodrome. *Neurotoxicity research. 2013; 24*(2), 216-243.

17. Zhang, X., & Le, W. Pathological role of hypoxia in Alzheimer's disease. *Experimental neurology. 2010; 223*(2), 299-303.

18. Ju, Y. E. S., Finn, M. B., Sutphen, C. L., et al. Obstructive sleep apnea decreases central nervous system–derived proteins in the cerebrospinal fluid. *Annals of neurology. 2016; 80*(1), 154-159.

19. Baril, A.-A., Gagnon, K., Brayet, P., et al. Gray matter hypertrophy and thickening with obstructive sleep apnea in middle-aged and older adults. *American journal of respiratory and critical care medicine. 2017; 195*(11), 1509-1518.

20. Mason, M., Welsh, E. J., & Smith, I. Drug therapy for obstructive sleep apnoea in adults. *Cochrane Database of Systematic Reviews*(5). 2013.

21. Buchman, A. S., & Bennett, D. A. Loss of motor function in preclinical Alzheimer's disease. *Expert review of neurotherapeutics. 2011; 11*(5), 665-676.

22. Troussière, A.-C., Charley, C. M., Salleron, J., et al. Treatment of sleep apnoea syndrome decreases cognitive decline in patients with Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry. 2014; 85*(12), 1405-1408.

23. Cooke, J. R., Ayalon, L., Palmer, B. W., et al. Sustained use of CPAP slows deterioration of cognition, sleep, and mood in patients with Alzheimer's disease and obstructive sleep apnea: a preliminary study. *Journal of clinical sleep medicine. 2009; 5*(4), 305-309.

24**.** Yo-El S. Ju, Brendan P. Lucey and David M. Holtzman. Sleep and Alzheimer disease pathology—a bidirectional relationship. 2013.