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Is It Time to Consider Obstructive Sleep Apnea Syndrome a Risk Factor for Alzheimer's Disease?

Obstructive sleep apnea syndrome (OSAS) is a highly prevalent sleep disorder that has several consequences. As was recently documented, the prevalence of moderate-to-severe sleep-disordered breathing (⩾15 events/h) is 23.4% in women and 49.7% in men (1). These data, from a population-based study in Switzerland, reveal the real incidence of OSAS in the general population. OSAS has been consistently demonstrated to be a clinically relevant chronic sleep disorder characterized by recurrent episodes of upper-airway obstruction causing intermittent hypoxemia and hypercapnia, brain cortical microarousals and sleep fragmentation, increased inflammation, and oxidative stress (2). These features of OSAS have significant cardiovascular, neurocognitive, and metabolic consequences. Consequently, OSAS has been independently associated with several disorders, including hypertension, diabetes, metabolic syndrome, osteoporosis, and cardiovascular diseases (3–7). Moreover, OSAS has been identified as a risk factor for the development of Alzheimer's disease (AD) dementia (8).

Sleep disorders are currently being investigated as possible pathogenic factors that trigger neurodegenerative disorders, with particular attention being paid to their effects on AD pathology. The recent identification of the glymphatic system has led researchers to investigate the association between sleep and the risk of neurodegeneration (9). The group led by Ricardo S. Osorio has focused over the past few years on the interconnections between OSAS and AD pathology in populations of cognitively normal elderly individuals (10, 11). As a result of their investigations, OSAS was demonstrated to be responsible for cerebrospinal fluid (CSF) AD biomarker changes in the elderly (10). Moreover, they showed that OSAS is associated not only with a pathological reduction of CSF β-amyloid$_{42}$ (Aβ_{42}) levels but also with a continuing cognitive decline in the elderly (11). This evidence has been supported by further research, and it has been hypothesized that OSAS alters brain β-amyloid metabolism and promotes amyloid plaque deposition (12, 13). Therefore, the recent scientific literature has identified OSAS as a possible risk factor for AD neurodegeneration (12, 13).

The study by Sharma and colleagues (pp. 933–943) in this issue of the *Journal* represents an important milestone in this field (14). The authors first performed a longitudinal study analyzing the effect of OSAS on both CSF Aβ_{42} levels and brain amyloid burden in cognitively normal elderly subjects. Specifically, a large population of cognitively intact people (55–90 yr old) underwent OSAS monitoring by home polygraphic recording, followed by lumbar puncture for CSF biomarker analysis (Aβ_{42} and tau protein levels), and/or Pittsburgh compound positron emission tomography scans to detect brain amyloid deposition. These assessments were longitudinally repeated in a subgroup of subjects who underwent follow-up investigations. The main result of this study was the direct correlation observed between the annual rate of change of CSF Aβ_{42} concentrations and the apnea–hypopnea index. Secondarily, the authors confirmed that OSAS is a frequent diagnosis in adult and older people, as it affected 53% of the entire cognitively normal community-dwelling cohort. Moreover, the authors proved that the apnea–hypopnea index has a more significant association with the longitudinal change of β-amyloid measures than the apolipoprotein E4 genotype, which is currently

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considered one of the most important risk factors for sporadic AD. Finally, considering that not all patients have cognitive deterioration or brain magnetic resonance imaging structure pathological changes, the authors concluded that CSF $A\beta_{42}$ longitudinally decreases before the occurrence of signs or symptoms of AD. Notwithstanding the novelty of their results, the authors' explanation for the association between OSAS and AD is still speculative. However, different mechanisms that affect brain β-amyloid dynamics and thus induce AD pathological changes have been recognized in OSAS patients. In keeping with this observation, not only dysregulation of the glymphatic system but also intermittent hypoxemia, sleep fragmentation, slow-wave sleep impairment, synaptic dysfunction, brain inflammation, and Valsalva maneuvers (related to apnea events) may concurrently impair β-amyloid metabolism and clearance, causing the initial reduction of CSF $A\beta_{42}$ levels and subsequently the brain deposition of β-amyloid plaques (8–14).

These findings highlight the importance of diagnosing OSAS in late life, because it can pathologically change brain β-amyloid metabolism and subsequently induce AD neurodegeneration. It has been consistently demonstrated that CSF $A\beta_{42}$ levels decrease several years before brain magnetic resonance imaging structural changes and cognitive decline occur, supporting the hypothesis that OSAS may alter AD biomarkers in preclinical stages, which represent a possible temporal window in which therapeutic interventions may significantly change the course of the disease.

As a consequence, OSAS may be considered a risk factor for AD. However, in contrast to other demonstrated risk factors for the development of AD, this disorder can be treated by clinical interventions that are currently available in clinical practice. OSAS is easily treated by continuous positive airway pressure (CPAP), which usually ameliorates OSAS symptoms (15). In a recent investigation, the results of neuropsychological testing, CSF AD biomarkers, and sleep architecture were compared between untreated patients with OSAS and CPAP-treated patients with OSAS (15). Significantly, no signs of AD pathology were documented in the CPAP-treated patients, whereas CSF $A\beta_{42}$ levels were pathologically reduced in more than half of the untreated patients. Therefore, it was presumed that OSAS is associated with early but possibly modifiable AD biomarker changes (15). In support of this hypothesis, a very recent report documented the case of a middle-aged man who was affected by subjective cognitive decline coupled with OSAS (16). The subject underwent a lumbar puncture that revealed pathological CSF $A\beta_{42}$ levels, but had normal Pittsburgh compound and 2-deoxy-2-(18F) fluoro-D-glucose positron emission tomography scans. After CPAP treatment was initiated, the patient was followed for 1 year, with resolution of subjective cognitive complaints and normalization of CSF $A\beta_{42}$ concentrations. This case report has opened new horizons for considering AD biomarkers as changeable if treatment is initiated in the preclinical stage of the disease, when CSF β-amyloid metabolism and clearance are altered but brain β-amyloid plaques have not yet been deposited.

In conclusion, the impressive data published by Osorio and colleagues, coupled with recent observations presented in the literature, suggest a new direction in considering OSAS as a trigger factor for the development of AD. The next step is to verify in randomized clinical trials that CPAP treatment can prevent or reverse pathological changes in AD biomarkers during the preclinical stages of the disease, as alterations in β-amyloid brain clearance occur earlier than plaque accumulation, neuronal dysfunction, and clinical symptoms. ■

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