Self-reported sleep and Alzheimer disease CSF biomarkers

A wake-up call

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Alzheimer disease (AD) is the most prevalent cause of dementia, and numerous studies have described sleep disturbances and circadian abnormalities in persons with symptomatic AD.[1] A rapidly accumulating body of research suggests that disturbed sleep is not only a consequence of pathologic brain changes of AD, but may also contribute to AD pathophysiologic mechanisms, even in the preclinical stages of AD.[2] Sleep disturbances are associated with amyloid deposition, the first known stage of preclinical AD. Poorer sleep quality, as measured by wrist actigraphy, and more frequent napping were tied to CSF evidence of amyloid deposition,[3] and self-report of poorer sleep quality and shorter sleep duration were associated with greater amyloid burden, measured by amyloid PET imaging.[4,5] The hypothesized underlying mechanism is sleep-related decreases in soluble β-amyloid (Aβ) levels: sleep disturbance acutely increases soluble Aβ in humans and mice,[6] and chronically increases deposition of Aβ into plaques in mouse models.[7] Insufficient sleep is therefore a plausible promoter of amyloid deposition.

In this issue of *Neurology*®, Sprecher et al.[8] present evidence linking sleep disturbance to markers of neuropathology beyond amyloid deposition. The authors assessed the relationship of CSF markers of amyloid pathology (Aβ42:Aβ40 ratio), tau pathology (phosphorylated tau), neuronal injury (total tau, neurofilament light [NFL]), neural inflammation (monocyte chemoattractant protein-1 [MCP-1], chitinase-3-like protein 1 [YKL-40]), and synaptic dysfunction (neurogranin) to self-reported sleep measures in 101 middle-aged and older adults in the Wisconsin Registry for Alzheimer's Prevention. The 3 primary sleep measures were based on the 12-item Medical Outcomes Study (MOS) sleep scale, and included sleep adequacy, a 2-item measure of quality and quantity of nocturnal sleep; somnolence, a 3-item measure of daytime sleepiness; and sleep problems, a broad measure of nocturnal and daytime symptoms that also overlaps with the first 2 measures. The authors found that lower Aβ42:Aβ40 levels, suggesting greater amyloid pathology, were associated with worse sleep adequacy, consistent with prior studies.[3–5] They additionally found that increased phosphorylated tau, total tau, NFL, MCP-1, and YKL-40—all reflecting greater neuropathology—were associated with either or both somnolence and sleep problems. Notably, with the exception of total tau, these biomarkers' associations with sleep problems were significant only when expressed as ratios relative to Aβ42, which the authors suggest are better measures of cumulative AD pathology. In the current pathologic model of AD, amyloid deposition occurs first (preclinical AD stage 1), but tau pathology, synaptic dysfunction, and other neurodegenerative processes (preclinical AD stage 2) are necessary for cognitive symptoms to emerge.[9] Thus, Sprecher et al. have provided further evidence for a link between disturbed sleep and AD that extends beyond amyloid plaques, to include markers of active neuronal damage and inflammation that suggest imminent cognitive decline. Their findings suggest that while nocturnal sleep may be disturbed early in the process of amyloid deposition, daytime somnolence may be a sign of neurodegeneration and a window of opportunity for intervention.

Notably, Sprecher et al. did not find associations between any CSF markers and daytime somnolence as measured by the Epworth Sleepiness Scale (ESS), a widely used and validated measure of daytime sleepiness. The discrepancy between findings involving the 8-item ESS and the 3-item somnolence subscale of the MOS Sleep Scale may be explained by the different types of sleepiness assessed: the somnolence subscale assesses overall subjective daytime sleepiness and napping frequency, while the ESS specifically assesses for falling asleep (or, per Sprecher et al., "irresistible" sleepiness). Therefore, the ESS may not be sufficiently sensitive to detect mild hypersomnolence that does not cause unintentional dozing, and alternative measures of sleepiness may be required to identify sleep–wake dysfunction associated with preclinical AD. In addition, the sleep problems subscale was associated with a number of CSF markers, but these results are difficult to interpret because sleep problems queries multiple overlapping dimensions of

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sleep–wake and circadian function. Indeed, this study's use of lesser-known and subjective measures of sleep, with some subscales comprising only 2 or 3 items, is arguably its greatest limitation. An additional limitation is the lack of objective assessment of sleep-disordered breathing (SDB), which has been associated with CSF measures of both amyloid and tau pathology,[10] and increased risk of cognitive decline.[11] SDB commonly results in snoring and excessive daytime sleepiness, and while a single item on snoring was not associated with any CSF markers, the Somnolence subscale was associated with several, and those associations may be driven by SDB. Because SDB is one of the most common, and treatable, causes of sleep disturbance in the older population, the lack of information about SDB limits the study's robustness.

Sprecher et al. present data that extend previously described associations between amyloid plaques in preclinical AD and nocturnal sleep disturbance, to include associations between markers of neurodegeneration and daytime somnolence. Further studies with more robust self-reported sleep measures and —as the authors suggest—objective sleep–wake measures and longitudinal designs are needed to confirm these findings and clarify the directionality between sleep disturbances and AD neurodegenerative processes. Effective interventions are available to treat causes of poor sleep, so identifying and treating sleep disturbances in preclinical AD may be a critical strategy to prevent or delay impending cognitive decline.

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