SLEEP AND NEURODEGENERATION: A STATE OF THE ART REVIEW

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Learning Objectives

1. Review sleep and circadian disturbances in aging and neurodegenerative diseases, particularly Alzheimer Disease (AD)
2. Discuss the potential bi-directional relationship between sleep disruption and AD pathology.
3. Review associations between obstructive sleep apnea and AD.

I. Scope of sleep/circadian disturbances in neurodegeneration

- A. Normal aging is associated with changes in sleep and circadian function [1-2]
  1. Advance in circadian phase and decreased circadian amplitude
  2. Decrease in slow wave activity (SWA), increased N1 (light non-REM) sleep, slight decrease in REM sleep
  3. Increased frequency of arousals, decreased sleep efficiency
  4. Increase in prevalence of sleep disorders such as obstructive sleep apnea and restless legs syndrome
- B. In symptomatic Alzheimer Disease (AD) sleep/circadian disturbances are very common and bothersome, resulting in high cost of care both directly and indirectly for caregivers [3-4]
  1. AD is the most common cause of dementia. The lifetime risk of individuals reaching age 65 is 20% for women and 17% for men.
  2. Exaggerated trends in sleep that are seen in aging, including decreased sleep time, reduction in REM sleep, sleep fragmentation at night.
  3. Slowing of EEG and excessive sleepiness during wake periods
  4. In community-dwelling AD, 25-40% of patients have sleep/wake disturbances, and sleep/wake disturbances increase in severity and prevalence with AD severity.
  5. Delay in circadian phase and decrease in circadian amplitude are characteristic. Eventually, complete deterioration of circadian rhythm occurs in severe AD.
  6. Sundowning, or agitation in the evening, is difficult to treat and places a substantial burden to caregivers
  7. Nighttime wandering and wakefulness raise safety concerns and also create high caregiver distress; wake behaviors at night are often the reason for institutionalization.
  8. AAN Dementia Quality Improvement Measurement Set [5]
     a) Specifically addresses sleep and circadian disturbances under Neuropsychiatric symptom assessment and Depressive symptom screening
     b) Does not specifically mention sleep and circadian disturbances (although certainly relevant) under Safety counseling, Driving risk Counseling, and Caregiver education/support
- C. Preclinical AD, prior to any cognitive symptoms, is also associated with sleep disturbance.
  1. Amyloid pathology is associated with sleep disturbance [6-10]
  2. Sleep fragmentation associated with decreased cortical gray matter volume [8,10]
  3. APOE ε4 alone is associated with objective (but not subjective) sleep disturbance in a healthy older population [11]

II. Amyloid and Tau, and how they relate to sleep

- A. Alzheimer Disease is pathologically characterized by amyloid plaques and Tau tangles.
- B. Amyloid-β (Aβ) is released by neurons during synaptic activity, and normally remains soluble until it is cleared by a variety of mechanisms. Aggregation of soluble amyloid-β into insoluble amyloid plaques is the first known step in AD pathogenesis. [12-14]

1. As amyloid plaques form, they act as a “sink” for soluble Aβ, particularly the more toxic Aβ42 form. Decrease in cerebrospinal fluid Aβ42 is the first known biomarker of preclinical AD, followed closely by amyloid imaging.
2. Areas of the brain experimentally with higher levels of synaptic activity, and therefore higher Aβ levels, have higher levels of amyloid plaque deposition.
3. Regions of the brain most vulnerable to amyloid plaque deposition in AD co-incide with those areas most active during wakefulness, the Default Mode Network.

C. Amyloid-β (soluble) decreases during sleep and increases during wake, as demonstrated in mouse AD models as well as in humans CSF. [15-16]
1. Aging is associated with decreased amplitude of Aβ diurnal variation, and amyloid plaque deposition appears to eliminate this diurnal variation
2. Diurnal variation may be related to differences in rate of production and/or of clearance of Aβ during sleep vs wake.

D. The glymphatic system, which is a clearance mechanism for metabolites in the interstitial space, is most active during sleep, particularly SWA. Aβ clearance rates during sleep was 2x that during wakefulness.[17]

E. Effect of sleep deprivation on Aβ and amyloid plaques
1. Mouse AD models: acute sleep deprivation increases Aβ, and chronic sleep deprivation increases number of amyloid plaques [15]
2. Human study of total sleep deprivation for one night showed higher Aβ CSF levels compared to group without sleep deprivation.[18]

F. Sleep deprivation alters Tau metabolism and increases Tau accumulation in mouse [19-20]

II. <u>Potential bidirectional relationship between sleep disturbance and AD pathology</u> [21]

A. Amyloid plaque pathology may lead to abnormalities in sleep function
1. In a mouse AD model, sleep abnormalities occurred as amyloid plaques formed. Following treatment with antibodies against amyloid to clear plaques, normal sleep was restored.[22]
2. In humans, amyloid burden in the medial prefrontal cortex is associated with disrupted SWA and memory consolidation function. [23]
3. Interaction of sleep and Aβ in modulating neuronal excitability [24]

B. As previously noted (section I.C.), there are associations between amyloid deposition and disrupted sleep in preclinical AD. It is possible that this association is due to AD pathology leading to disrupted sleep, rather than the other way around. While multiple studies have shown a relationship between poor sleep quality or abnormal duration and development of cognitive problems, since AD has a long preclinical period, it is impossible to know from these studies the direction of causality.

C. A recent study showed sleep disruptions in a mouse AD model that does *not* have amyloid plaques or Tau tangles, suggesting that other AD pathological mechanisms may lead to sleep disruption.[25]

D. Amyloid deposition/AD pathology may affect circadian function and thereby secondarily affect sleep. [26] Retinal amyloid deposition and its effects on light input to the suprachiasmatic nucleus should also be considered. [27-28]

E. Overall, there is increasing evidence for a positive feedback loop where AD pathology worsens sleep/circadian function, and worse sleep hastens/accelerates AD pathology.

F. Additional confounders/interactions between sleep, AD pathology, cognitive performance
1. Sleep deprivation worsens cognitive performance, all things being equal
2. In mouse AD model, chronic sleep disruption worsened cognitive performance. [29]
3. Potential interaction of amyloid deposition and sleep disturbance [30]

G. A recent meta-analysis showed that people with sleep disturbance had 1.68 (95% CI 1.51-1.87)x risk for cognitive impairment and/or AD. → ~15% of AD may be attributed to sleep problems. [31]

III. <u>Obstructive sleep apnea</u>

A. OSA is a common sleep disorder, characterized by collapse of the upper airway during sleep, leading to recurrent cycles of decreased/cessation of airflow, hypoxia, hypercarbia, and arousals. Sleep-disordered breathing (SDB) encompasses OSA and other abnormalities of breathing during sleep.

B. Strong association between AD and SDB/OSA, in cross-sectional studies as well as prospective studies. In the two prospective studies, it seems that measures of hypoxia are what are related to poor cognitive outcomes, rather than measures of arousals/ sleep fragmentation.[32-34]

C. Potential mechanisms linking OSA to AD
   1. Glymphatic clearance: Decreased clearance of amyloid/tau related to pressure changes during apneas [35]
   2. Cerebrovascular: OSA is associated with worse vascular outcomes (hypertension, cardiovascular disease, possibly stroke risk). It is possible that microvascular brain disease contributes to or accelerates cognitive decline [36-37]
   3. Cognitive: OSA and worse sleep quality in general may lead to worse cognitive function, making it more likely that someone with an existing level of brain pathology will be considered to have symptomatic dementia. [38-40]
   4. AD pathology: Chronic intermittent hypoxia (a model of OSA) has been shown to increase Aβ generation in mouse models. Hypoxia also has been shown to increase expression of β-site amyloid precursor protein cleaving enzyme (BACE), leading to increased Aβ levels. [41-42]
   5. Inflammatory pathways, stress response, mitochondrial dysfunction, and other [43]

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