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Sleep in Alzheimer's Disease–Beyond Amyloid

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ABSTRACT

Sleep disorders are prevalent in Alzheimer's disease (AD) and a major cause of institutionalization. Like AD pathology, sleep abnormalities can appear years before cognitive decline and may be predictive of dementia. A bidirectional relationship between sleep and amyloid β (Aβ) has been well established with disturbed sleep and increased wakefulness leading to increased Aβ production and decreased Aβ clearance; whereas Aβ deposition is associated with increased wakefulness and sleep disturbances. Aβ fluctuates with the sleep-wake cycle and is higher during wakefulness and lower during sleep. This fluctuation is lost with Aβ deposition, likely due to its sequestration into amyloid plaques. As such, Aβ is believed to play a significant role in the development of sleep disturbances in the preclinical and clinical phases of AD. In addition to Aβ, the influence of tau AD pathology is likely important to the sleep disturbances observed in AD. Abnormal tau is the earliest observable AD-like pathology in the brain with abnormal tau phosphorylation in many sleep regulating regions such as the locus coeruleus, dorsal raphe, tuberomammillary nucleus, parabrachial nucleus, and basal forebrain prior to the appearance of amyloid or cortical tau pathology. Furthermore, human tau mouse models exhibit AD-like sleep disturbances and sleep changes are common in other tauopathies including frontotemporal dementia and progressive supranuclear palsy. Together these observations suggest that tau pathology can induce sleep disturbances and may play a large role in the sleep disruption seen in AD. To elucidate the relationship between sleep and AD it will be necessary to not only understand the role of amyloid but also tau and how these two pathologies, together with comorbid pathology such as alpha-synuclein, interact and affect sleep regulation in the brain.

Contents

Abbreviations: Aβ, amyloid β; AD, Alzheimer's disease; APP, amyloid precursor protein; BF, basal forebrain; bvFTD, behavioral variant FTD; CBD, corticobasal degeneration; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; DR, dorsal raphe; EDS, excessive daytime sleepiness; EEG, electroencephalography; FTD, Frontotemporal Dementia; htau, human tau; ISF, interstitial fluid; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamus; mPB, medial parabrachial nucleus; NBM, nucleus basalis of Meynert; NFT, neurofibrillary tangle; NREM, non-rapid eye movement; PAG, periaqueductal gray matter; PLMD, periodic limb movement disorder; PPT, pedunculopontine tegmental nucleus; PSP, progressive supranuclear palsy; PFZ, parafacial zone; RBD, REM sleep behavior disorder; REM, rapid eye movement; SCN, suprachiasmatic nucleus; SLD, sublaterodorsal area; SWS, slow wave sleep; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus; vPAG, ventral periaqueductal gray

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1. Introduction

For over 25 years, a high prevalence of sleep disorders has been identified in patients with Alzheimer's disease (AD). Many studies have estimated that 25–66% of AD patients exhibit sleep disorders of some kind and sleep disturbances are one of the leading causes of AD patient institutionalization (Bianchetti et al., 1995; Guarnieri et al., 2012; Moran et al., 2005). Sleep is an important biological function and although sleep disturbances were once considered to be a bi-product of neurodegeneration, they are not limited to advanced disease states but occur even before cognitive decline and may be predictive of neurodegeneration (Hahn et al., 2013; Lim et al., 2013). AD pathology has been shown to begin long before the onset of the clinical cognitive impairment characteristic of AD. The preclinical stage of AD is characterized by the aggregation of amyloid-β (Aβ) peptide into amyloid plaques in the brain and a decrease of $A\beta_{42}$ in the cerebrospinal fluid (CSF) as well as tau phosphorylation and aggregation into neurofibrillary tangles (NFT) and neuropil threads in neocortical regions (Holtzman et al., 2011). This molecular pathology, especially tau pathology, is then linked with neuronal death, synaptic loss, cognitive impairment, and AD diagnosis (Jack and Holtzman, 2013; Holtzman et al., 2011). The presence of sleep disturbances throughout preclinical and clinical disease progression underscores the important role sleep may play in disease pathology and progression.

Studies in humans and mouse models have begun to unravel the relationship between sleep, AD, and cognitive impairment, but much work remains. Due to the abundance of mouse models that develop amyloid deposition and biomarker tests available, much is known about the bidirectional interaction between sleep, Aβ, and its aggregation in the brain. However, to fully understand the interaction between AD and sleep, the contribution of tau and other pathologies cannot be ignored. Here, we will review the clinical relationship between AD and sleep and how amyloid pathology contributes to this interaction. We will further highlight how tau pathology in AD may interact with sleep disturbances including evidence from tauopathies such as frontotemporal dementia (FTD). Lastly, up to 60% of AD patients also have the presence of alpha-synuclein aggregation in the brain and we will highlight ways in which this pathology may contribute to sleep disturbances seen in AD as well as similarities between AD and dementia with Lewy bodies (DLB)(Hamilton, 2000).

2. Sleep and circadian disturbances in AD patients

AD patients exhibit a wide array of sleep, electroencephalography (EEG), and circadian dysfunction that is well reviewed in the literature (Musiek et al., 2015; Peter-Derex et al., 2015; Lim et al., 2014b). Excessive daytime sleepiness (EDS), sundowning, and insomnia are among the most common reported disturbances in AD and stem from changes in sleep architecture and circadian rhythm. AD patients have been shown to have decreased sleep efficiency, non-rapid eye movement (NREM) sleep and slow wave sleep (SWS) as well as decreased rapid eye movement (REM) sleep and increased latency to REM sleep (Vitiello et al., 1990; Bliwise et al., 1989; Bonanni et al., 2005). Consequently, AD patients display an increase in wakefulness that is characterized by an increased number of awakenings at night (Moe et al., 1995; Vitiello et al., 1990; Bonanni et al., 2005). Taken together these changes result in an observed increase in sleep fragmentation in AD patients (Vitiello et al., 1990). Sleep disturbances are found to occur throughout clinical disease with most changes visible in mild disease stages and these disruptions worsen with disease severity (Vitiello et al., 1990; Bonanni et al., 2005; Liguori et al., 2014b). Increased REM sleep latency and wakefulness as well as decreased REM sleep and sleep efficiency are also found to correlate with impaired cognitive function (Moe et al., 1995; Liguori et al., 2014b). The abundance of sleep disturbances in AD patients even in early stages of cognitive impairment may be due to neuronal and synaptic loss that is already occurring at these stages of disease.

Prior to clinical diagnosis, sleep disturbances are also a risk factor for developing cognitive dysfunction and AD. A recent study in a preclinical population has shown using actigraphy that a decrease in sleep efficiency is visible even in cognitively normal people that are amyloid positive compared to those that are amyloid negative, suggesting a role for Aβ aggregation in preclinical sleep changes (Ju et al., 2013). Furthermore, clinical follow up studies have shown that cognitively normal older individuals with high sleep fragmentation had a 1.5-fold increased risk of developing AD and self-reported reduced sleep was associated with a 2-fold increased risk of AD development (Hahn et al., 2013; Lim et al., 2013). These early, preclinical changes in sleep suggest that poor sleep may be a risk factor and biomarker for AD and cognitive decline and demonstrates that pathological AD-type changes may be leading to sleep abnormalities prior to obvious cognitive symptoms. This supports the idea that sleep disruption may be prognostic for future cognitive decline.

Changes in sleep architecture are also accompanied by changes in EEG power. Quantitative EEG studies show that AD patients exhibit EEG slowing in both wake and REM sleep that increases with disease severity and suggest that REM sleep EEG slowing is a robust biomarker for AD severity (see (Petit et al., 2004) for in-depth review). Markers of circadian dysfunction have also been identified in AD patients and include increased nocturnal activity, decreased diurnal activity, core body temperature phase delay and amplitude decrease, clock gene phase changes across brain regions, and changes in sleep regulating hormones such as decreased nocturnal melatonin (sleep promoting) and increased hypocretin/orexin (wake promoting) (Volicer et al., 2001; Harper et al., 2005; Liguori et al., 2014b; Wu et al., 2003; Cermakian et al., 2011). The relationship between AD progression and sleep modulating hormones is not straightforward however. Studies have shown that CSF orexin levels in moderate to severe AD are significantly increased compared to controls and high orexin levels were appropriately associated with increased nocturnal disturbance (Liguori et al., 2014b). However, post mortem analysis shows decreased hypocretin in the CSF and a 40% reduction in hypocretin −1 immunoreactive neurons in the hypothalamus

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