Exploring the Link Between Sleep, Beta-Amyloid Accumulation, and Neuroinflammation in Alzheimer's Disease: Implications for Prevention and Treatment

Nicholette Touserkani, Isabella Lassalle, Aris Yang, Sarah Jones, Amber Mach, Kaitlyn Gilbride, Stephanie Kim, Anton Dao

Public Health and Health Sciences, Undergraduate Lab at Berkeley

University of California, Berkeley

Table of Contents

Abstract

Dysregulated sleep is often a typical companion of Alzheimer's disease and other forms of dementia, but the exact relationship between the two remains complex. Beta-amyloid (Aβ) is a protein related to the onset of dementia, with high levels of Aβ plaque buildup being positively correlated with Alzheimer's disease, but it is unclear by which mechanism Aβ causes dementia. Recent studies have suggested a bidirectional relationship between sleep disturbances and Alzheimer's pathology, wherein disrupted sleep may prevent the clearing of Aβ plaque from the extracellular space, thus exacerbating Aβ accumulation and vice versa, creating a cycle that accelerates cognitive decline. Continuously activated microglia may play a role in the development of neurodegenerative diseases. Microglia are the main sources of brain inflammation, and thus, research indicates that excessively activated microglia can generate elevated levels of proinflammatory cytokines and chemokines, which are neuroimmune inflammatory factors that ultimately result in impaired neuronal function. The emphasis on early disease stages is pivotal in highlighting treatments targeting later stages as well, particularly dementia. While addressing early stages is crucial, it is just as important to address and develop symptomatic treatments for advanced disease stages. Our research highlights various approaches to addressing the various stages of Alzheimer's disease. Current studies focusing on non-pharmacological prevention are increasingly utilizing evidence-based multimodal intervention programs that coincide with lifestyle changes and sleeping habits. Other pharmaceutical therapies including drugs that target Aβ plaque and others that modulate neuroinflammatory pathways are also being implemented. In addition, immunotherapy has also proven to be useful as it employs both active and passive strategies in formulating anti-beta-amyloid antibodies. Our analysis and research seek to combine various methods of

interventions to mitigate AD while seeking to find improved study designs for more effective preventive outcomes.

Introduction

Understanding the complex interplay between sleep disorders and neurocognitive impairment is crucial in clinical practice, as both are prevalent yet frequently overlooked conditions. Despite an estimated 70 million Americans suffering from sleep disorders, these conditions are diagnosed in under 3.5% of patients in primary care settings (Shenker & Singh, 2017). Similarly, neurocognitive disorders are often underdiagnosed, with a study revealing that only a quarter of patients with moderate to severe impairment had their condition noted in medical charts (Shenker & Singh, 2017). Moreover, these two conditions frequently co-occur, with daytime sleepiness being an independent risk factor for neurocognitive decline, and a significant portion of patients with cognitive impairment also meeting criteria for a sleep disorder. This overlap underscores the importance of further research into sleep disorders and their impact on neurocognitive function, highlighting the need for increased awareness and recognition of these conditions in clinical practice.

Past papers have found that a lack of sleep among middle and old-aged folks is correlated with dementia and Alzheimer's Disease (Sabia et al., 2021), which will be referred to as AD from here on out in this paper. This is a very serious issue because sleep disorders and neurocognitive disorders are intertwined, but they are often missed in clinical practice. As a note to physicians, if a sleep order is diagnosed, then extra care should be taken to see if there are any neurological disorders and vice versa.

The protein beta-amyloid (denoted Aβ) seems to be the culprit of this phenomenon. Researchers have shown that there is an association between lack of sleep and this protein. Essentially, losing sleep can increase the amount of Aβ in the brain, and researchers believe that the buildup of Aβ is associated with AD (Kojori et al., 2018). However, it is unclear if removing this plaque in the brain will cure the disease at this time. This paper will try to fill in this gap and examine studies that look at this issue to see if these new therapies can work.

Microglia, the resident immune cells of the central nervous system (CNS), have emerged as a focal point in AD research. These cells play a crucial role in nerve development by engulfing and clearing damaged neurons and synapses. However, in the context of AD, activated microglia can adopt a proinflammatory phenotype, leading to the production of harmful substances. Our research aims to explore the role of neuroinflammation and microglial phenotype in AD pathology, highlighting their potential as both diagnostic markers and therapeutic targets in AD treatment.

Methods and Procedures

Given our initial goal to investigate an association between sleep and dementia, as well as therapeutic approaches connected to the sleep-related disorders, early search terms utilized in gathering papers included “sleep” and “dementia therapeutics” in the past 15 years. We excluded any studies that focused on data before 2009 to make sure our findings were as up to date and relevant as possible . Once we found a common discussion about Beta amyloid, and Microglia in the abstracts of our initially sourced articles which were published after 2009, “B-amyloid” and “microglia” became additional search terms we used in finding related research papers. Additionally, to make sure the articles we used contained information directly relating sleep to

dementia, we would use terms like “sleep and dementia”, and “sleep and Alzheimer's” to also encompass all neurodegenerative diseases that fall under dementia.

To evaluate whether there is a compelling link between sleep and dementia, the assessment of an individual’s Default Mode Network (DMN) must be considered. The DMN is a widely distributed neurocognitive network of anatomically connected brain regions that tend to become active or quiescent together, by default, when a person is awake but disengaged, as when one lets one’s mind wander. Functional magnetic resonance imaging (fMRI) can be used to assess an individual’s DMN (Shenker & Singh, 2017). The link between REM behavior disorder (RBD) and neurodegenerative Parkinsonism demonstrates a promising connection between sleep disorder and dementia-causing disease. Longitudinal studies of people with RBD were performed to see if they would later develop neurodegenerative Parkinsonian disease. These studies involved clinical evaluation of RBD emerging in patients and over 5,000 studies that evaluated possible risk factors (Shenker & Singh, 2017).

To further examine the relationship between sleep and dementia risk, we decided to look at data from a longitudinal study to see how different sleeping patterns contribute to microglial activity over time. A key idea we wanted to address was how microglia may engage in repair processes during the early stages of AD, and how in late-onset AD (LOAD), microglia might exhibit harmful behavior by releasing proinflammatory molecules that contribute to neuronal damage. Longitudinal studies taking a person’s year to year approach during the span of three years determined the age-specific incidence rate of developing dementia, which is calculated by dividing the number of dementia cases by the number of person-years at risk during a 3-year time interval. In addition, more short-term research using positron emission tomography (PET) and F-florabetan was also used to measure an individual’s length of sleep in one night, which is

used in correspondence to their sleeping history to collect data for Aβ burden (ABB). Calculations using a t-test are then used to determine ABB concentrations in different areas of the brain after sleep deprivation.

Data

From 1985 through 1988, 10,308 people were recruited to participate in a study relating the length of sleep to dementia risk (Séverine Sabia et al). The subjects were split into three subgroups according to their age (50, 60, and 70 years). For each group, the age-specific incidence rate of developing dementia was determined using the person-years approach, which is calculated by dividing the number of dementia cases by the number of person-years at risk during the 3-year time interval. For those who were 50 years old, the incident rate of developing dementia was 2.8 per 1000 persons-years if the participants slept less than or equal to six hours per night (P = 0.04), 2.4 per 1000 persons-years if the participants slept seven hours per night (reference), and 3.0 per 1000 persons-years if the participants slept greater than or equal to eight hours per night (P = 0.07). For participants who were 60 years old, the incident rates were 4.7 per 1000 persons-years for less than or equal to six hours of sleep (P = 0.005), 3.2 per 1000 persons-years for seven hours of sleep (reference), and 3.6 per 1000 persons-years for greater than or equal to eight hours of sleep (P = 0.34). For participants who were 70 years old, the incident rates were 9.3 per 1000 persons-years for less than or equal to six hours of sleep (P = 0.10), 6.8 per 1000 persons-years for seven hours of sleep (reference), and 8.1 per 1000 persons-years for greater than or equal to eight hours of sleep (P = 0.60) (see *Table 1).*

	N cases/*N* total	Incidence rate per 1000 persons-years	Model 1: adjusted for sociodemographic variables[a]		Model 1 + behavioural factors[b]		Model 1 + health-related factors[c]		Fully adjusted model	
			HR (95%CI)	*P* value[d]	HR (95%CI)	*P* value[d]	HR (95%CI)	*P* value[d]	HR (95%CI)	*P* value[d]
Sleep duration at age 50[e]	521/7959									
Short: ≤6 h	211/3149	2.8 (2.4–3.2)	1.28 (1.06–1.55)	0.01	1.27 (1.05–1.54)	0.01	1.22 (1.01–1.48)	0.04	1.22 (1.01–1.48)	0.04
Normal: 7 h	219/3624	2.4 (2.1–2.7)	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Long: ≥8 h	91/1186	3.0 (2.4–3.7)	1.25 (0.98–1.59)	0.08	1.25 (0.98–1.60)	0.07	1.24 (0.97–1.59)	0.09	1.25 (0.98–1.60)	0.07
Sleep duration at age 60[e]	409/7164									
Short: ≤6 h	192/2759	4.7 (4.0–5.4)	1.48 (1.19–1.84)	<0.001	1.46 (1.17–1.82)	0.001	1.38 (1.11–1.73)	0.004	1.37 (1.10–1.72)	0.005
Normal: 7 h	142/2988	3.2 (2.7–3.7)	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Long: ≥8 h	75/1417	3.6 (2.8–4.4)	1.15 (0.87–1.52)	0.33	1.17 (0.88–1.55)	0.28	1.13 (0.85–1.50)	0.39	1.15 (0.87–1.52)	0.34
Sleep duration at age 70[e]	392/6516									
Short: ≤6 h	171/2429	9.3 (7.9–10.7)	1.33 (1.06–1.68)	0.004	1.29 (1.03–1.63)	0.005	1.26 (1.00–1.60)	0.04	1.24 (0.98–1.57)	0.10
Normal: 7 h	131/2578	6.8 (5.6–7.9)	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Long: ≥8 h	90/1509	8.1 (6.4–9.7)	1.22 (0.94–1.60)	0.39	1.13 (0.91–1.55)	0.34	1.18 (0.90–1.55)	0.22	1.15 (0.88–1.51)	0.60

Table 1: Association between sleep duration at 50, 60, and 70 years and incidence of developing dementia, N cases/N total = 426/6875 (data by Séverine Sabia et al.)

Sabia et al. also divided the individuals into six subgroups related to their sleep time: persistent short (≤ six hours), persistent normal (seven hours), persistent long (≥ eight hours), change from short to normal (≤ to six hours to seven hours), change from normal to long (seven hours to ≥ eight hours), and change from normal to short (7 hours to ≤ to six hours). The same person-years approach of calculating the age-specific incidence rate of developing dementia was used for this study. For participants who identified under the persistent short category, there was an incident rate of developing dementia of 10.5 per 1000 persons-years (P = 0.048), for those

under the persistent normal category, there was a rate of 7.3 per 1000 persons-years (reference), and for those under the persistent long category, there was a rate of 9.9 per 1000 persons-years (P = 0.20). For participants who identified under the change from short to normal category, there was an incident rate of developing dementia of 8.2 per 1000 persons-years (P = 0.23), for those under the change from normal to long category, there was a rate of 7.1 per 1000 persons-years (P = 0.90), and for those under the change from short to normal category, there was a rate of 9.6 per 1000 persons-years (P = 0.50). (see *Table 2*)

Trajectories of sleep duration between age 50 and 70[a]	*N* cases/*N* total	Incidence rate per 1000 persons-years	Model 1: adjusted for sociodemographic variables[b]		Model 1+ behavioural factors[c]		Model 1+health-related factors[d]		Fully adjusted model	
			HR (95%CI)	*P* value[e]	HR (95%CI)	*P* value[e]	HR (95%CI)	*P* value[e]	HR (95%CI)	*P* value[e]
Persistent short	103/1358	10.5 (8.5–12.5)	1.40 (1.08–1.81)	0.01	1.35 (1.05–1.75)	0.02	1.32 (1.02–1.72)	0.03	1.30 (1.00–1.69)	0.048
Persistent normal	141/2520	7.3 (6.1–8.5)	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Persistent long	35/461	9.9 (6.6–13.1)	1.32 (0.91–1.91)	0.15	1.27 (0.88–1.85)	0.20	1.32 (0.91–1.91)	0.15	1.28 (0.88–1.85)	0.20
Change from short to normal	61/1086	8.2 (6.1–10.2)	1.23 (0.91–1.66)	0.18	1.21 (0.90–1.64)	0.21	1.21 (0.90–1.64)	0.21	1.20 (0.89–1.63)	0.23
Change from normal to long	47/946	7.1 (5.0–9.1)	1.04 (0.75–1.45)	0.81	1.03 (0.74–1.44)	0.85	1.03 (0.74–1.44)	0.86	1.02 (0.73–1.42)	0.90
Change from normal to short	39/504	9.6 (6.6–12.6)	1.21 (0.84–1.73)	0.30	1.17 (0.82–1.68)	0.38	1.15 (0.80–1.65)	0.44	1.13 (0.79–1.62)	0.50

Table 2: Association of trajectories of sleep duration (using data on sleep duration at 50, 60, and 70 years, N cases/N total = 426/6875, data by Séverine Sabia et al.) with the incidence of developing dementia

It has been known that there seems to be some association between the buildup of β-amyloid (Aβ) in the brain and AD. There have also been studies done to see the relationship between sleep deprivation and the buildup of β-amyloid (Aβ) in the brain. In a particular study done by Ehsan Shokri-Kojori et al., researchers examined the relationship between sleep deprivation and the buildup of Aβ burden (ABB), which is just the clearance of Aβ (Kojori et al., 2018). To do this, they looked at how one night of sleep deprivation affects the clearance of Aβ

in the brain. Researchers looked at 20 healthy individuals who were aged between 22 and 72 years old, and 10 of them were female. They then looked at individuals with poor sleep history and how that would affect ABB. To measure the amount of Aβ, the researchers used positron emission tomography, PET, and ^{18}F-florbetaben to measure. Using the t-test, they found that there were statistically significant ABB increases in a right lateralized cluster that comprised hippocampal, parahippocampal, and thalamic regions (5% increase, $P < 0.0001$) from one night of sleep deprivation.

Many clinical trials regarding the development of dementia treatment are ongoing, including a recent study from clinicaltrials.gov, which assessed the agents in the pipeline for dementia treatment for phase I, phase II, and phase III clinical trials. They found that there are 105 agents in the dementia treatment pipeline, of which 25 agents are in 29 trials in Phase I, 52 agents are in 68 trials in Phase II, and 28 agents are in 42 trials in Phase III. A majority of the drugs in the pipeline (70%) are disease-modifying therapies (DMTs) directed at amyloid-related targets. In the study completed by clinicaltrials.gov, for example, of the 25 agents in Phase I, 12 DMTs were used, 12 of which were directed at amyloid-related targets. Of the 52 agents in Phase II, 36 DMTs were used, 14 of which were directed at amyloid-related targets. Of the 28 agents in phase III, 18 DMTs were used, 15 of which were directed at amyloid-related targets.

Among the different approaches targeted at beta-amyloid in the drug development pipeline for dementia treatment, immunotherapy remains the best-developed strategy. Within immunotherapy, there are two types of treatments directed at beta-amyloid: active and passive. Janssen and Pfizer, two pharmaceutical companies, are currently testing active therapy to monitor the effects of their new beta-amyloid vaccine, ACC-001. Novartis Pharmaceuticals is also doing the same with their new vaccine, CAD106. AFFiRiS AG, a research institution, and

AC Immune, a clinical-stage biopharmaceutical company, are currently running tests related to active immunotherapy and the pursuit of amyloid-related targets.

On the other hand, passive immunotherapy for dementia is focused on prevention and early treatment, and there are many companies involved in this groundbreaking research. For example, Eisai, a research-based pharmaceutical company, is conducting phase II clinical trials with patients experiencing early dementia by introducing them to anti-beta-amyloid antibodies to stop the progression of the disease. Biogen, a biotechnological company, is also conducting clinical trials at the level of phase I. They too plan to utilize anti-beta-amyloid antibodies to halt disease development. The immunotherapy treatment of dementia is ongoing. New studies will produce more data, but as this research is fairly new, the data is very limited.

In the meantime, several studies have looked at active treatment already to see if removing Aβ is effective. A study performed by Mengian Pang et al. was conducted to test this hypothesis (Pang et al., 2022). This study pools data from 16 randomized trials where subjects had a 0.1 unit decrease in PET Aβ SUVR (Standard Uptake Value Ratio). They found with 95% confidence that participants lowered their scores in various methods of quantifying dementia, including the Alzheimer's Disease Assessment Scale (0.034 - 0.15), Cognitive Subscale (0.12 - 0.55), and the Mini-Mental State Examination (0.017 - 0.024). Overall, there was statistically significant evidence that reducing Aβ plaques caused a reduction in cognitive and functional decline in AD patients.

However, another project led to a different conclusion. Sarah Ackley et al. had essentially the same goal as the previous study and had a similar methodology (Ackley et al., 2021). They pooled results from the 14 randomized controlled trials and looked at the reduction of amyloid levels by 0.1 SUVR units. What they found with 95% confidence was that the mini-mental state

examination score increased by -0.06 to 0.1 points. Because zero was contained in this confidence interval, no statistically significant conclusion could be made when determining if reducing Aβ in the brain leads to better cognitive function.

Several studies have revealed that lack of sleep increases dementia risk, and the amount of risk increases with age. People with persistently short sleep are at the greatest risk with 95% confidence, while those under other identifications, such as a change from receiving persistently long sleep to short amounts of sleep, yield no meaningful results. It has also been known that the buildup of Aβ is related to the development of AD, so lots of treatments target this protein. However, these studies present conflicting results; with one claiming that removing Aβ improved cognition, while another suggesting that there were no statistically significant conclusions to be drawn.

Discussion

The amyloid cascade hypothesis stands as one of the foundational theories in understanding the pathogenesis of AD. It posits that the misfolding and aggregation of β-amyloid (Aβ) peptides play a central role in initiating a cascade of events leading to neurodegeneration and cognitive decline. This hypothesis has garnered significant attention and remains a focal point in both basic research and clinical investigations into AD. Aβ peptides are derived from the amyloid precursor protein (APP) through sequential cleavage by β- and γ-secretases. Under normal conditions, Aβ peptides are cleared from the brain through various mechanisms, including enzymatic degradation and clearance via the glymphatic system. However, in AD, there is an imbalance between production and clearance, leading to the accumulation of Aβ peptides and the formation of insoluble plaques in the brain parenchyma and vasculature.

Activated microglia, the resident immune cells of the central nervous system, play a crucial role in the response to Aβ accumulation. Microglia are responsible for the phagocytosis and clearance of Aβ peptides, as well as the release of proinflammatory cytokines and chemokines. While microglial activation initially serves a protective function by attempting to clear Aβ aggregates, prolonged activation can lead to chronic inflammation and neuronal damage.

The involvement of neuroinflammation in AD pathology extends beyond microglial activation. Astrocytes, another type of glial cell, also contribute to the neuroinflammatory response through the release of cytokines and reactive oxygen species. Additionally, there is evidence of peripheral immune cell infiltration into the brain, further exacerbating the inflammatory milieu in AD. Recent advancements in neuroimaging techniques have provided insights into the dynamic changes occurring in the brain during AD. Functional magnetic resonance imaging (fMRI) studies have revealed alterations in neural network connectivity, particularly within the default mode network (DMN), which is implicated in various cognitive functions, including memory and attention. Disruptions in DMN connectivity have been observed in individuals with AD and those at risk for developing the disease, suggesting a potential biomarker for early detection and monitoring of disease progression.

In light of the amyloid cascade hypothesis and the role of neuroinflammation in AD, therapeutic strategies targeting Aβ accumulation and neuroinflammatory processes have been pursued. One approach involves the development of Aβ-targeting therapies, such as monoclonal antibodies and small molecule inhibitors, aimed at reducing Aβ plaque burden in the brain. Clinical trials evaluating the efficacy of these therapies have shown promising results, with some demonstrating a reduction in amyloid burden and slowing of cognitive decline in AD patients.

In addition to Aβ-targeting therapies, there is growing interest in modulating neuroinflammatory pathways as a potential therapeutic strategy for AD. Preclinical studies have identified various targets within the neuroinflammatory cascade, including microglial activation pathways and proinflammatory cytokines, as potential candidates for drug development. Furthermore, repurposing existing anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and immunomodulatory agents, for AD treatment is being explored.

Despite the promising advancements in AD therapeutics, significant challenges remain in translating preclinical findings into effective treatments for patients. The complexity of AD pathology, heterogeneity of patient populations, and limited understanding of disease mechanisms pose barriers to successful drug development. Additionally, the multifactorial nature of AD necessitates a multifaceted approach to treatment, targeting not only Aβ accumulation but also other pathological processes, such as tau protein aggregation, synaptic dysfunction, and neuroinflammation.

The amyloid cascade hypothesis and the role of neuroinflammation in AD provide valuable insights into disease pathogenesis and potential therapeutic targets. While significant progress has been made in understanding and treating AD, continued research efforts are needed to develop effective therapies that can halt or slow disease progression. A comprehensive approach, integrating both Aβ-targeting and neuroinflammatory-modulating strategies, holds promise for advancing the field of AD therapeutics and improving outcomes for patients affected by this devastating disease.

Conclusions

Common sleep disturbances significantly impact dementia risk and progression, so it is essential to address these disorders as part of comprehensive dementia management strategies. Beta-amyloid accumulation and microglial activation are central to the pathogenesis of dementia, offering potential targets for therapeutic interventions. Emerging drugs targeting Aβ plaques show promise in slowing disease progression, although their clinical significance warrants further investigation. Therefore, a comprehensive understanding of the complex mechanisms underlying sleep-dementia interactions is essential for developing effective prevention and treatment strategies for dementia. Studies consistently show a negative correlation between inadequate sleep duration and dementia risk, emphasizing the importance of addressing sleep disturbances as a potential preventive measure. The role of Beta-Amyloid in dementia pathology underscores the need for targeted therapeutic approaches aimed at reducing beta-amyloid burden in the brain. While recent advancements in drug development offer promising avenues for intervention, ongoing research is necessary to confirm the clinical significance of these treatments and explore alternative strategies. Understanding the intricate interplay between microglial activation, neuroinflammation, and synaptic loss provides valuable insights into disease mechanisms and potential diagnostic markers. As research continues to illuminate the connections between sleep disorders and dementia, it becomes evident that encompassing both preventive measures and targeted interventions is paramount in the fight against neurodegenerative diseases.

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