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The potential and prospects of sleep biomarkers in early Alzheimer's disease diagnosis

Xiuyun Li

College of Science, Zhejiang A&F University, Hangzhou, Zhejiang, China, 201203

lixyctw@outlook.com

Abstract. Alzheimer's disease (AD), often accompanied by sleep disturbances, is a neurodegenerative disease. Sleep disruptions have the potential to serve as biomarkers for early diagnosis because they can be observed in the initial stages of disease progression in the sleep-wake cycle. This paper summarizes the latest findings on AD manifestations during non-rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep, sleep oscillations, and cognitive impairment. It provides a detailed overview of diagnostic bioindicators for primary Alzheimer's disease, including invasive cerebrospinal fluid (CSF) markers, non-invasive electroencephalography (EEG), and plasma biomarkers, and compares their advantages and limitations in diagnosing early AD. The accuracy and reliability of sleep biomarkers in early diagnosis are evaluated, along with their clinical application prospects. The paper also proposes improvements in the use of sleep clinical markers for early Alzheimer's disease diagnosis, aiming for greater breakthroughs in this field. The significance of this review lies in its in-depth exploration of the association between sleep disturbances and the early period of the disease, along with the introduction of potential biomarkers that can serve as tools for early determining and monitoring of this neurodegenerative health issue.

Keywords: Alzheimer's disease (AD), non-rapid eye movement (NREM), rapid eye movement (REM), electroencephalography (EEG).

1. Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder closely attached to cognitive impairment and dementia in individuals aged 65 and older worldwide, significantly impacting public health [1, 2]. The hallmark pathological features of AD include insoluble deposits of β-amyloid (Aβ) in the extracellular space and the accumulation of highly phosphorylated microtubule-associated protein tau into neurofibrillary tangles within neurons [3]. Synaptic and neuronal damage happen before cognitive symptoms and pathological signs become evident and continue for 10-20 years [3]. Symptoms of AD typically manifest in late life, and currently, there are ineffective treatments to reverse the medical symptoms and pathological alterations of AD [4]. This places a substantial financial and caregiving burden on patients and their families. Therefore, early detection of AD is crucial for disease monitoring and early intervention. Research has indicated that sleep-wake disorders are typical in AD patients and are associated with cognitive impairment [5]. Since these sleep abnormalities are often observed in the

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preclinical stages, they may serve as potential biomarkers for detecting AD. Furthermore, to prevent or slow the progression of AD, targeting sleep for early intervention should be considered [6].

Over the years, exploring early biomarkers of AD has become a hot topic in research. The primary research strategy involves correlating sleep-related indicators, blood-related markers, and pivotal Alzheimer's disease cerebrospinal fluid (CSF) bioindicators, such as amyloid-β(Aβ42), total tau (T-tau), and phosphorylated tau (P-tau), in healthy individuals, those with modest cognitive dysfunction, and AD clients, to identify the most strongly correlated markers [1,2]. Some progress has been made in these studies, but there are also challenges for clinical application, such as the risks, costs, accuracy, and accessibility of the detection methods. This paper summarizes the manifestations of AD in different sleep stages, recognizing that early-stage presentations vary among individuals but share common characteristics, such as reduced slow-wave activity (SWA) during non-rapid eye movement (NREM) sleep and diminished rapid eye movement (REM) sleep duration [6,7]. Additionally, it analyses the potential prospects for the clinical adoption of invasive cerebrospinal fluid (CSF), non-invasive electroencephalography (EEG), and plasma biomarkers for early diagnosis. As research advances, the accuracy and reliability of sleep biomarkers have significantly improved. Due to their ease of operation, suitability for long-term monitoring, and potential for large-scale early AD screening, sleep biomarkers hold promise for widespread clinical use.

2. Alzheimer's Disease Manifestations in Different Sleep Stages

2.1. Non-Rapid Eye Movement (NREM) Sleep and Alzheimer's Disease

Non-rapid eye movement (NREM) sleep refers to the sleep stage without rapid eye movement, which can be divided, based on electroencephalogram (EEG) monitoring, into sleep onset, the unconscious stage (occasionally characterized by faster sleep spindle and K-complex waves), delta waves (δ-waves), and slow-wave sleep (deep sleep). Both animal models and human research have revealed a correlation between reduced slow-wave activity (SWA) during NREM sleep and amyloid-β(Aβ) accumulation. Studies on cognitive performance, neuroimaging, and cerebrospinal fluid (CSF) levels in aging participants with AD have shown a negative correlation between NREM SWA and tau pathology, especially in the 1-2 Hz frequency range. This could aid in distinguishing tau pathology from cognitive impairment in the pre-symptomatic or earliest stages of AD [7]. In addition to the reduced slow-wave activity during NREM sleep, decreased theta and sigma activity, and changes in spindle characteristics, have been found to have a strong connection to the risk of cognitive disorders [8]. NREM sleep is crucial for optimal memory function, and research reports indicate frequency-specific deficits in frontal slow waves during NREM sleep in the context of AD pathology [9,10]. Recent studies suggest that deep NREM slow-wave sleep (SWS) can enhance learning and memory function in older adults who are in good health and potentially mitigate impaired memory resulting from a substantial burden of AD pathology [11].

2.2. Rapid Eye Movement (REM) Sleep and Alzheimer's Disease

Rapid Eye Movement (REM) sleep, usually referred to as paradoxical sleep (PS) or desynchronized sleep, is a sleep time where the activity of brain neurons resembles wakefulness, characterized by rapid, low-voltage desynchronized brainwaves. Reduced REM sleep duration and slower oscillations during REM sleep have been observed in AD patients [6], with typical AD cases showing impaired N3 sleep and relatively preserved REM sleep [5]. Through entropy measurements and cognitive function assessments during wakefulness and sleep states, it has been found that the slow-fast activity ratio (SFAR-entropy) is most pronounced in the temporal and occipital regions of the brain's EEG, effectively distinguishing dementia from healthy controls. This effect is most prominent during rapid eye movement (REM) sleep, which is associated with high acetylcholine activity [12].

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2.3. Sleep Oscillations and Cognitive Impairment in Alzheimer's Disease

Recently, medical studies have suggested that changes in the function of GABAergic neurons within the cortex, hippocampus, and thalamic reticular nucleus mediate changes in sleep oscillations in AD. These changes may affect sleep-dependent memory consolidation or the restorative function of sleep and could potentially serve as targets for interventions [6]. Memory-related neural circuits generate oscillatory events in single-channel sleep electroencephalograms (EEG), including theta rhythm bursts (TBs), sleep spindles (SPs), and various subtypes of slow waves (SWs). An analysis of data from 205 elderly adults, including sleep EEG, Alzheimer's disease-related biomarkers in cerebrospinal fluid, and clinical dementia assessment scales, revealed that cognitive impairment was related to reduced spectral power in TBs. Individuals with normal cognition but positive for amyloid-β showed lower accuracy in the coupling of certain neural circuits, and the coupling of some neural circuits was correlated with biomarkers in cerebrospinal fluid, such as Aβ42/Aβ40, phosphorylated tau181, and total tau [13].

3. The Potential of Sleep Biomarkers as Early Diagnostic Tools

3.1. Invasive Cerebrospinal Fluid (CSF) Diagnostic Biomarkers

Cerebrospinal fluid (CSF) is a clear liquid found in the subarachnoid space of the central nervous system [14]. It contains proteins and glucose and plays a crucial role in clearing metabolic waste, including important Alzheimer's disease bioindicators like amyloid-β (Aβ42), total tau (T-tau), and phosphorylated tau (P-tau). These biomarkers are highly valuable for the early diagnosis of the disease [15]. However, collecting CSF samples involves a procedure called lumbar puncture [16], which can be complex, require skilled professionals, and yield limited sample quantities. It can also be painful and carry a risk of cerebrospinal fluid leakage, especially for certain patients [14,17]. Additionally, this invasive CSF examination is expensive and is typically more suitable for later stages of the disease [18].

3.2. Non-Invasive Electroencephalography (EEG) Diagnostic Biomarkers

Electroencephalography (EEG) has been a fundamental tool for monitoring sleep abnormalities and assessing cognitive function in dementia patients for many years [19]. EEG, as a non-invasive method for comprehensive measurement of neuronal activity, stands as a primary candidate functional biomarker for synaptic dysfunction and loss in dementia. Research has indicated alterations in sleep structure in people with Alzheimer's disease (AD), with anomalous EEG patterns particularly evident during both rapid eye movement (REM) and non-rapid eye movement (NREM) sleep stages [5,11]. Detecting abnormal neuronal activity patterns associated with different stages of AD, EEG signals reached over 70% precision in classifying individuals into three categories: HC (healthy controls), MCI (mild cognitive impairment), and AD (Alzheimer's disease). Therefore, EEG can be a valuable tool for preliminary assessment for the diagnosis of MCI and AD, as well as for assessing disease progression [20].

3.3. Plasma Biomarkers

Plasma biomarkers related to Alzheimer's disease pathology have seen rapid development in recent years. Robust blood detection methods have been established for amyloid and tau pathology, neurodegeneration, and astrocyte activation [21]. Researchers have compared ten assay methods for p-tau181, p-tau217, and p-tau231, identifying plasma phosphorylated tau (p-tau) as one of the most hopeful blood biomarkers for Alzheimer's disease [22]. Recent studies exploring the relationship between plasma and traditional AD biomarkers have identified P2X7 and TNAP as novel plasma diagnostic markers for MCI and AD [23].

4. Discussion

Currently, international guidelines for diagnosing Alzheimer's disease (AD) recommend the use of medical indications and cerebrospinal fluid (CSF) biomarkers, with the three core CSF biomarkers being Aβ1-42, total tau protein (t-tau), and phosphorylated tau at position 181 (p-tau181). Cerebrospinal fluid

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marker screening involves the somewhat invasive procedure of lumbar puncture, which collects up to 30 milliliters of CSF. Typical adverse effects of lumbar puncture include dorsal pain and headaches, with occasional serious complications such as subdural hematoma, cerebral venous thrombosis, and infections. Experts suggest the use of cerebrospinal fluid proportions to enhance the speediness and accuracy of AD diagnosis and forecast development from mild cognitive impairment (MCI) to AD. Essentially, CSF diagnostic markers offer details about amyloid and tau markers. Additionally, the financial cost of CSF proportions testing is 10-15 times less than that of PET imaging. Then, obtaining CSF analysis reports from medical chemistry laboratories may take a considerable amount of time [24].

In recent years, there has been intensive research into detecting blood biomarkers to predict or improve the diagnosis of AD. Conversely, the potential blood-based markers discovered thus far have certain shortcomings, most of which are correlated to the specified detection technologies. Therefore, efforts should be made to identify stable and easily detectable blood biomarkers to enhance AD diagnosis and better differentiate AD from mild cognitive impairment (MCI) [23].

Sleep, as a non-invasive and repeatable physiological measure, can provide a new avenue for early Alzheimer's disease diagnosis. However, more research is still needed to clarify the accuracy and reliability of sleep biomarkers in early diagnosis. Sleep biomarkers are easy to operate, suitable for long-term monitoring, and can facilitate large-scale screening for early AD [19]. Sleep is influenced by various factors, such as stress and environment, which can lead to the complexity of results. It is advisable to integrate various non-invasive health indicators, including heart rate variability, eye movements, and respiratory patterns, to potentially improve diagnostic accuracy and reliability. Long-term biomarker monitoring can capture sleep change trends more accurately and distinguish normal aging from pathological changes [25]. Utilizing machine learning and artificial intelligence (AI) techniques to analyze a large amount of sleep data can uncover potential patterns and features, thereby enhancing diagnostic accuracy [26]. The method of utilizing interpretable artificial intelligence (AI) in conjunction with high-density electroencephalography (HD-EEG) achieved an accuracy rate of 98.97% in testing patients with cognitive impairment. This research represents a breakthrough in traditional EEG limitations within Alzheimer's disease studies, offering not only a potential early diagnostic approach but also a profound understanding of EEG changes during the progression of AD. Consequently, this fusion of AI and EEG presents new prospects and hope for Alzheimer's disease research [27].

Sleep biomarkers hold significant clinical application prospects as a potential method for early AD diagnosis. Despite current challenges, through further research and improvements, we are likely to unlock the full potential of sleep biomarkers in early AD diagnosis, providing patients with earlier and more precise interventions and treatments.

5. Conclusion

This paper summarizes the connection between Alzheimer's disease (AD) and sleep disturbances, highlighting the potential of sleep disturbances as biomarkers for early AD. The paper discusses the manifestations of AD in different sleep stages, including the characteristics of non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM). It emphasizes the association of reduced slow-wave activity (SWA) in NREM sleep with decreased REM sleep duration in AD patients. Sleep oscillations and cognitive impairment in AD are also discussed, playing a crucial role in early AD diagnosis.

Furthermore, the paper introduces different types of early AD diagnostic markers, including invasive cerebrospinal fluid (CSF) markers, non-invasive electroencephalogram (EEG) markers, and plasma markers. CSF markers have a certain level of accuracy in early AD diagnosis but come with invasiveness and high costs. EEG markers offer a non-invasive method suitable for screening and diagnosing mild cognitive impairment (MCI) and AD. Finally, research into plasma markers is advancing, although technical and accuracy-related challenges need to be addressed.

In summary, sleep biomarkers hold significant clinical application prospects as a potential method for early AD diagnosis. While challenges remain, further research and improvements in sleep

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biomarkers may provide a more accurate and reliable tool for the early diagnosis of AD, enabling earlier interventions and treatments.

This review study, while referencing recent literature, has limitations in terms of the breadth and depth of its conclusions due to the limited number of citations. Additionally, the use of large-scale sleep monitoring data can raise ethical and privacy concerns, important issues that are not thoroughly discussed in the article. Although the paper cites experimental data from other research, it does not conduct a credible assessment of the reliability of this data. Furthermore, the article mentions the prospective application of machine-based learning and automated intelligence technologies in analyzing sleep data but does not provide specific methods and cases, lacking a description of technical details.

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