

Sleep and Cognitive Decline: A Strong Bidirectional Relationship. It Is Time for Specific Recommendations on Routine Assessment and the Management of Sleep Disorders in Patients with Mild Cognitive Impairment and Dementia

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Key Words

Sleep disorders · Hypersomnolence · Circadian rhythm sleep disorders · Sleep disordered breathing · Parasomnias · Restless legs syndrome · Dementia · Sleep recommendations

Abstract

Background: Sleep disturbances and disruption of the neural regulation of the sleep-wake rhythm appear to be involved in the cellular and molecular mechanisms of cognitive decline. Although sleep problems are highly prevalent in mild cognitive impairment (MCI) and many types of dementia, they have not been systematically investigated in the clinical setting and are often only investigated by sleep specialists upon individual request. **Summary:** This review discusses sleep disorders in the context of cognitive decline and provides an overview of the clinical diagnosis and management of these disorders in patients with dementia and MCI. **Key Messages:** Sleep disorders are largely underestimated and do not receive sufficient attention in the global management of dementia patients. Sleep disturbances have a significant impact on cognitive and physical functions in individuals with cognitive decline and may be associated with important psychological distress and depression. They are positively associated with the severity of behavioral problems and cognitive im-

pairment. **Clinical Implications:** The recent recommendations by the Sleep Study Group of the Italian Dementia Research Association can be used as a guideline for the clinical assessment and management of sleep disorders in MCI and dementia patients. Sleep disorders should be carefully investigated using an in-depth sleep history, physical examination, questionnaires and clinical scales and should be validated with the support of a direct caregiver. The recommendations for older adults can be used as a framework to guide the diagnosis and treatment of sleep disorders in individuals with dementia and MCI. The management strategy should be based on the choice of different treatments for each sleep problem present in the same patient, while avoiding adverse interactions between treatments.

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Introduction

Several studies have suggested that sleep and sleep-wake rhythm disturbances are associated with an increased risk of incident dementia and cognitive decline in the elderly, independent of multiple confounders [1–5]. Abnormalities in sleep architecture have been described in mild cognitive impairment (MCI), and they interfere with sleep-dependent memory consolidation, thus con-

tributing to memory impairment [6]. In preclinical Alzheimer disease (AD), amyloid depositions as assessed by cerebrospinal fluid (CSF) amyloid beta (A β) 42 levels seem to be associated with lower sleep quality [7]. In Lewy body dementia and Parkinson disease (PD), sleep disorders, including daytime hypersomnolence and nocturnal parasomnias, and rapid eye movement (REM) behavior disorder (RBD) have been recognized to be prodromal features and may contribute to the typical fluctuations of the disease. Thus, their treatment may improve disease fluctuations and the patient's quality of life [8–10].

Normal aging is associated with a decline in the consolidation of sleeping and waking patterns. Some healthy older adults, but particularly dementia patients, often nap during the daytime and experience fragmented sleep at night. AD patients exhibit many sleep disturbances in the earliest stages of the disease and about 50% of them may experience prevalent changes in circadian rhythm [11–16].

Sleep is a dynamic process involving a network of state-modulating neurons in the hypothalamus and brain stem; homeostatic and circadian systems interact to create daily periods of stable sleep and wakefulness [17]. Alterations in the sleep–wake cycle seem to be the result of changes in several functions, including the core body temperature cycle, abnormal melatonin circadian rhythm and reduced melatonin secretion [18, 19], decrease in light exposure, degeneration in melanopsin-expressing retinal ganglion cells [20] and dysregulation of several other genes [21, 22].

The suprachiasmatic nucleus of the hypothalamus plays a central role in controlling circadian sleep–wake rhythms, but it is not the only brain pacemaker; other local semi-autonomous clocks are distributed across the brain – in the cerebral cortex, hippocampus and cerebellum [23]. An abnormal functioning of the suprachiasmatic nucleus has been described in AD patients and visual and retinal abnormalities as early manifestations of retinal A β plaque pathology have been detected in AD patients, animal models and in preclinical AD [24, 25]. However, a recent study failed to demonstrate beta-amyloid, phospho-tau and alpha-synuclein deposits similar to those in the brain in the eyes of AD and PD patients. This suggests that these deposits are either not found in the eye in a manner analogous to that in the brain or are present in different forms [26]. Further studies are needed in order to clarify the relationship between abnormalities in the brain and in the eyes of AD and PD patients and how these may be affected by sleep dysfunction. Cholinergic connections of the brain stem also seem to be involved in

the sleep–wake rhythm dysregulation detected early in clinical and preclinical AD patients [27].

Several studies have focused on the contribution of the genetic control of sleep toward cognitive decline. The rhythmic expression of BMAL1, CRY1 and PER1 in the cingulate cortex, bed nucleus of the stria terminalis and/or pineal gland appears to be lost in clinical and preclinical AD patients [21, 22, 28]. On the other hand, Tseng et al. [29] examined the expression of PER1 in circulating leukocytes across different sleep phases in healthy subjects and in MCI and AD patients, but found no differences. Further studies are needed to elucidate the exact interaction between CLOCK genes and other pathogenic factors in dementia patients such as amyloid levels, neurofibrillary tangles, oxidative stress, immune system function, lipidomic alterations, excitotoxicity and so forth. The genetic aspects of sleep are closely inter-related with environmental factors, and they also likely act in concert to contribute toward the clinical aspects of AD.

Hypothalamic polypeptides, such as melanin-concentrating hormone and hypocretin-1 (HCRT-1), promote sleep–wake regulation, energy homeostasis and they also seem to be involved in cognitive performance. They are synthesized in the hypothalamus, a region where senile plaques and neurofibrillary tangles are found. Experimental studies demonstrate that receptors for both peptides can also be found in areas typically affected in the AD patients, such as the cerebral cortex, basal forebrain, amygdala and brain stem [30, 31]. There is growing evidence of the impairment of melanin-concentrating hormone and HCRT-1 systems in AD patients, that is, in post-mortem studies of the hypothalamus of AD patients and controls, a decrease in cell number and lower CSF HCRT-1 levels were found. Gender differences in CSF HCRT-1 have also been found, supporting the higher prevalence of sleep disturbances and AD in women [30, 32, 33]. In both human and mouse models, the level of A β increases during wakefulness and decreases during sleep following a circadian rhythm and is regulated by orexin [34–36].

Recent animal studies indicate that the cortical interstitial space increases by more than 60% during sleep, resulting in an efficient convective clearance of A β and other compounds. Approximately, 65% of exogenously delivered A β is cleared by the glymphatic system and occur most efficiently during sleep. Therefore, sleep problems could contribute to the pathology of AD and to the progression of the disease. In mouse models of AD, chronic sleep deprivation augmented the formation of amyloid plaque, while increasing sleep with an orexin receptor antagonist reduced amyloid plaques [37].

Among community-dwelling older adults, self-reports of shorter sleep duration and poorer sleep quality have been associated with greater A β deposition measured by carbon 11-labeled Pittsburgh compound B positron emission tomography [38], suggesting that sleep problems per se might determine brain lesions and are not merely a consequence of dementia brain lesions [39].

Better sleep consolidation seems to attenuate the effect of the APOE genotype on incident AD and development of neurofibrillary tangle pathology. Assessment of sleep consolidation may identify APOE+ individuals at high risk for incident AD, and interventions to ameliorate sleep consolidation may aid in reducing the risk of AD and development of neurofibrillary tangles in APOE ϵ 4+ individuals [40, 41].

Therefore, disturbed sleep may increase soluble A β levels over the long term, leading to an increased possibility of deposition in amyloid plaques, further sleep disruption and, subsequently, symptomatic AD in a bidirectional relationship which needs to be further elucidated [42]. The same relationship between sleep problems and other non-A β -toxic metabolite production and clearance could mediate other aspects of the pathology of AD and other kinds of dementia. Numerous studies suggest an association between sleep-disordered breathing (SDB), cognitive decline and CSF AD biomarkers in cognitively normal elderly individuals. This suggests that therapies for SDB such as continuous positive airway pressure (CPap) could delay the onset of MCI or dementia [43–46].

Of the various types of SDB, obstructive sleep apnea (OSA) is more than 40% prevalent in patients with AD and other dementias [14–16]. OSA can induce neurodegeneration as a result of sleep fragmentation and intermittent hypoxia. As such, inflammation and cellular stress can impair cell–cell signaling, synaptic function and neural circuitry, thus leading to cognitive decline. Although clinical studies, neuroimaging, experimental animal evidence and molecular mechanisms suggest a causal relationship between OSA and AD, this relationship has not been completely demonstrated; further longitudinal studies are needed to determine whether SDB increases the severity of the disease in individual patients and whether it is associated with a more rapid progression of AD and other dementias [47].

In addition, OSA is associated with significant morbidity and mortality and is an independent risk factor for the development of cardiovascular disease, particularly hypertension, coronary artery disease, congestive cardiac failure and stroke [48, 49]. Consequently, detection of SDB is particularly relevant in vascular dementia (VaD) patients. The use of CPap has been shown to decrease

sleep disturbances in patients with AD and OSA, and some studies have shown positive improvement in neuropsychological functioning [50]. Overall, there is strong evidence supporting the need to identify and treat SDB in dementia whenever possible according to the compliance of the patient and the cooperation of the caregiver. This is also true for MCI and preclinical AD.

Taken together, these data suggest that early and progressive abnormalities in the sleep circadian rhythm, quality, architecture and neural regulation may be useful markers and prognostic indicators of cognitive decline and dementia. Further work is needed to identify the multiple causes, but there is growing evidence that they may influence one another with important implications on diagnosis and treatment [51].

Clinical Diagnosis and Management of Sleep Disorders in Cognitive Decline

Sleep disturbances are highly prevalent in community-dwelling patients with AD, and they are also common in other types of dementia such as frontotemporal dementia, VaD, Lewy body and PD dementia [9, 13–16, 52]. Despite their high frequency, pathogenetic role and clinical and social implications, sleep disturbances have not been systematically and carefully investigated in the clinical setting and thus are often underestimated.

In MCI and dementia patients, the major sleep complaints or disturbances include insomnia, hypersomnolence or excessive daytime sleepiness (EDS), circadian sleep–wake rhythm disturbances with sundowning, SDB, including OSA, primary central sleep apneas, Cheyne-Stokes breathing syndrome and sleep-related hypoventilation/hypoxemic syndrome, REM parasomnias, in particular RBD, restless legs syndrome/Willis-Ekbom disease and periodic limb movements [53].

The Sleep Study Group of the Italian Dementia Research Association (SINDem) multicenter sleep study on the prevalence of sleep disturbances in MCI and dementia disorder patients indicated that 2 or more sleep disturbances occur almost always in association in the same patient; the 2 most frequently found disturbances were insomnia and EDS in 10 and 8% of cases, respectively. Although these 2 disturbances were associated with each other at a high frequency, no specific pattern of association has emerged so far [16]. Since sleep disturbances tend to occur almost invariably in association, an accurate clinical investigation of the presence and type of sleep disorders is relevant for diagnosis and treatment.

Recommendations on Clinical Assessment and Management of Sleep Disorders in Patients with Cognitive Decline

The SINDem group recently prepared specific recommendations for sleep disorders in individuals with MCI and dementia, which were approved by the Italian Neurological Association on February 14, 2014 [54]. The recommendations are directed at professionals (primarily but not exclusively neurologists) involved in the complex diagnostic work-up of dementia patients; their aim is to establish uniform levels of care, to promote collaborative research into areas of uncertainty and to define the qualitative characteristics that distinguish dementia and sleep centers. These recommendations were prepared based on the available scientific evidence (i.e. the critical review of peer-reviewed scientific publications). The subjective professional judgment and opinions of the members of the SINDem group were only expressed in cases where empirical published evidence was either insufficient or contradictory.

The most important messages directed at clinicians involved in the diagnosis and treatment of cognitive decline are the following:

(1) Sleep disorders are frequent and tend to occur almost invariably in association in patients with cognitive decline; they must always be carefully investigated using an in-depth sleep history, physical examination, questionnaires and scales and should be validated whenever possible using acceptable and definite values of sensitivity and specificity, directly reported by the patient and with the support of the direct caregiver, whenever possible.

(2) Recommendations for older adults can be considered a good instrument also for persons with MCI and dementia when specific recommendations are unsatisfactory or insufficient.

(3) Instrumental supports for the assessment of sleep disturbances should be considered in selected patients, after referral to a sleep specialist.

Regarding the general management of sleep disorders in patients with dementia, the paper underlines that treatments are similar to those used in non-demented individuals of the same age. In addition, it is of utmost importance to consider any associated medical and psychiatric conditions. The management of sleep disturbances should be based on the choice of different treatments for each sleep problem present in the same patient, while avoiding adverse interactions between treatments. The authors suggest that particular attention be devoted to

EDS, circadian sleep-wake rhythm disturbances and their differential diagnoses.

Hypersomnolence or EDS is highly frequent in neurodegenerative disorders and is observed even in patients without night time problems; consequently, EDS should always be addressed in MCI and dementia patients, independently from other sleep disturbances. To investigate this, the clinical impression based on a detailed history and/or on the observations by caregiver or trained staff is fundamental, especially in patients with moderate to severe dementia. Whenever possible, according to the level of cognitive decline, subjective questionnaires such as the Epworth Sleepiness Scale can be used to assess the severity of EDS [55]. Referral to a sleep specialist should be undertaken when EDS might be related to central disorders of hypersomnolence such as narcolepsy or idiopathic hypersomnia [53].

Clinicians should always investigate for SDB in patients with cognitive decline showing EDS, in particular in nursing home residents and in VaD patients.

Video-polysomnography (PSG) is essential for detecting specific aspects of several sleep disturbances, particularly in REM and non-REM parasomnias, but the procedure is costly and requires appropriate monitoring equipment. Moreover, cognitively impaired patients are often uncooperative and intolerant of all monitoring devices. In many countries, the limited number of sleep centers makes PSG often unavailable even when it is clearly medically warranted. Consequently, in a routine clinical setting, clinicians can easily use questionnaires and scales that adequately screen for sleep disturbances. Regarding RBD for instance, in the Mayo Sleep Questionnaire, bed-partner/informant version of the question on possible RBD has been recently validated for individuals with cognitive decline. An affirmative response to the question was 98% sensitive and 74% specific for PSG-confirmed RBD; the specificity increased depending on the responses to additional questions if there was no history suggesting OSA [56]. The core question used in the Italian multicenter study to assess clinically probable RBD is similar to the Mayo Questionnaire and can also be used [54].

There are many recommendations about the management of sleep disturbances in the SINDem paper. Since several studies have demonstrated the risks and significant side effects of pharmacological treatments for insomnia in older individuals and in dementia patients [57], non-pharmacological treatments such as sleep hygiene, cognitive behavioral therapy and light therapy are recommended. The authors also consider ventilations for

SDB, suggesting that OSA patients with MCI or dementia have to be treated independently from age and cognitive impairment and that offering CPap treatment to patients who are able to comply and are assisted by a valid caregiver is a reasonable approach.

Conclusion

Sleep disturbances have a significant impact on cognitive and physical functions in individuals with cognitive decline and may be associated with important psychological distress and depression. They are positively associated with the severity of behavioral problems and cognitive impairment.

Despite the strong association between sleep disorders and cognitive and functional deterioration, there is very

little clinical data on this relationship. The latest evidence suggests that if sleep disorders are accurately diagnosed in the prodromal stage of dementia, appropriate treatments can be administered early on, and clinical and functional impairment may be delayed. These findings underscore the importance of collaboration between sleep experts, neurologists and researchers involved in the study of cognitive decline and dementias to expand our knowledge of this obscure field. As Prof. J. McKinley wrote, 'when we try to encourage a good night's sleep for our patients, perhaps we are doing them more good than we thought' [58].

Disclosure Statement

The authors have no conflicts of interest to declare.

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