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Review Article

Sleep disturbances and mild cognitive impairment: A review

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ARTICLE INFO

Article history:

Received 21 May 2014

Accepted 2 October 2014

Available online 23 February 2015

Keywords:

Sleep disturbance

Mild cognitive impairment

Sleep apnea

Dementia

Elderly

ABSTRACT

Objective: Mild cognitive impaired (MCI) is viewed as a transitional stage from normal to dementia. The aim of this study is analyze the sleep disturbances in subjects diagnosed as carries MCI.

Methods: A review of the literature was conducted in order to document sleeps problems in the context of MCI.

Results: Among the studies that compares the prevalence of sleep disturbances between subjects with MCI and those with normal cognition demonstrated that night time behaviors are more common in MCI patients (18.3–45.5%) than in normal population (10.9–23.3%).

Conclusions: Sleep disturbance is prevalent and predictive of cognitive decline in older people and in those with neurodegenerative disorders. The sleep problems have to be identified and treat to preserve the cognition and the MCI subjects with sleep disturbances have to be follow more closely to identify the initial signs of dementia.

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1. Introduction

Mild cognitive impaired (MCI) is viewed as a transitional stage from normal to dementia. Patients affected with this condition have a higher turn-over rate to Alzheimer's disease (AD) with the average rate of 10–15% annually over 5 year [1]. But which of these patients will evolve to AD? Which of these we have to follow more closely? And in the future, if disease-modifying drugs for AD became available, which patients will be chosen to take these medicines? Maybe the answer is in the comorbidities, particularly the neuropsychiatric ones.

The definition of this transitional stage was proposed by some authors like the National Institute of Mental Health that, in 1986, proposed the term age-associated memory impairment (AAMI) that characterize memory changes in ageing which were felt to be a manifestation of normal cognition [2]. But the most used concept is the one proposed by Petersen in 2004 [3]. The essential features of these criteria for MCI include: (i) memory complaint usually corroborated by an informant, (ii) objective memory impairment for age, (iii) essentially preserved general cognitive function, (iv) largely intact functional activities, (v) not demented. No particular test or cutoff score is specified. Beyond the

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Peer review under responsibility of Brazilian Association of Sleep.

definition, the author has been proposed clinical subtypes of MCI. The criteria described define the amnesic MCI subtype (aMCI) which is used for subjects who have memory impairment. If no memory impairment is present then the subject has non amnesic MCI (naMCI). After that, subject is classified in aMIC-single domain or naMCI-single domain if only a single domain (in case of aMIC is memory) is impaired or aMCI-multiple domain or naMCI-multiple domain if multiple domains are impaired (in aMCI it must be included memory). The most typical MCI patient is one who has memory impairment beyond what is expected to be normal for age but is relatively intact in other cognitive domains and this impairment is no sufficient severity to constitute dementia [3].

The specific transition between normal ageing and MCI can be quite subtle and the distinction between MCI and very early dementia can also be challenging. Thus, attempts for a combination of measures, clinical features, neuropsychological testing, biomarkers and neuroimaging may be the key to a more accurate diagnosis. Among clinical features, the neuropsychiatric symptoms have been extensively studied. The prevalence of these symptoms in MCI patients is around 50% while at subjects with normal cognition is approximately 25% [4,5]. Between neuropsychiatric symptoms the most common are apathy (11.7–68%), depression/dysphoria (20–56%), sleeping problems (18.3–56%) and anxiety (14.1–54%) [4–7]. The reported prevalence for subjects with normal cognition for apathy (0–4.8%), depression (11–16%), sleeping problems (10.9–23%) and anxiety (5.0–26.7%) is lower than for MCI individuals [4,7]. Although these symptoms are common in subjects with MCI it is uncertain if they can predict AD in this population, as a biomarker. The studies that try to answer this question found contradictory results for the relationship affective symptoms and AD [8–13]. Anyway, in any elderly patients with neuropsychiatric symptoms, we should not overlook the possibility of underlying cognitive impairment.

Sleeping problems are common in dementia. These problems can led to a worsening memory because the consolidation of memories are made during the sleep time. And the alterations in the person's brain with AD can led to alterations in sleep architecture [11]. The evaluation of sleep in those with supposed risk for dementia may be relevant and could be a potential target for early intervention. The aim of this study is analyze the sleep disturbances in subjects diagnosed as carries MCI, as a review of the studies published until this moment.

2. Method

A review of the literature was conducted in order to document sleeps problems in the context of MCI. An exhaustive MEDLINE and PUBMED search was performed for the period of 2002 and February 2013 for all article cross-referenced for "sleep disturbances" and "mild cognitive impairment". Additional search was conducted using the terms "neuropsychiatric symptoms". Only articles written in English or Portuguese were searched. A total of 8 studies were selected due to their relevance, methodology and accessibility. Of these 8 studies, 7 articles are clinical trials and 1 is a review article. Some studies were excluded because they analyzed the

neuropsychiatric symptoms but not analyzed clearly the sleep disturbances.

3. Results

3.1. Study design and setting

Among the 7 clinical trials, 3 reported cross-sectional data [4,5,7] and 4 used a longitudinal design [6,14–16]. In 2 of the longitudinal studies [14,15] the subjects were analyzed for 2 weeks, in 1 of them [16] the subjects were analyzed for 1 week and there is an article [6] that follow-up the subjects for 10 years. The subjects who participated were selected in memory or neurology clinics [6,14–16] or the authors used the data collected in a population-based samples [4,5,7].

The majority of the studies used the Petersen criteria for MCI [3]. Only 1 study [6] used Global Deterioration Scale [17] and another one [5] used the Statistical Manual of Mental Disorders, Fourth Edition (DSM-4) [18] and they classified as MCI the subjects that had some cognition impairment but not meeting DSM-4 for dementia. The cognition level was assessment by a test battery which is different in one study to another. All studies used the Mini Mental Scale Examination [19].

To access the presence and severity of neuropsychiatric symptoms the Neuropsychiatric Inventory (NPI) [20] was used at the cross-sectional studies. The NPI has scripted screening questions for each of 12 domains: sleep, depression, anxiety, delusion, agitation/aggression, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, hallucination and eating. If a positive response was obtained in any domain, then the standardized questions focusing on that positive feature would be used to explore the details of frequency (range 1–4) and severity (1,mild; 2,moderate; 3,severe).

Not all studies used questionnaires to access sleep disturbances. Two studies used actigraphy and one of them used polysomnographic to note not only the subjective complaints but also the objectives ones.

3.2. Prevalence of sleep disturbances

Among the studies that investigated the prevalence of sleep disturbances in a population, they found distinguishing features between subjects with MCI, those with normal cognition and AD patients. The study conducted by Muangpaisan compares subjects with and without cognitive impairment and demonstrated that night time behaviors are more common in MCI patients (45.5%) than in normal population (23.3%) [7]. Another study comparing the same both population report a prevalence of night time behaviors around 18.3% in individuals with MCI and 10.9% in individuals with normal cognition [4]. The article that used the Cardiovascular Healthy Study to compare individuals classified as having dementia, as having MCI and did not meet criteria for MCI and dementia found that 8.8% of MCI participants have sleep disturbance, comparing with 19.9% from AD patients, (the prevalence in normal population was not available). According to this article, sleep problems are the most frequent clinically

significant neuropsychiatric symptom and the second one among patients with dementia [5]. The other study that analyses people with dementia and compared with people with MCI found a prevalence of 37% of sleeping problem in the first group and 56% in the second group [6]. This conflicting results maybe be partially explained by the difference in scale used in the latter study.

The study that used the polysomnographic to compare sleep and memory in healthy older adults and MCI older adults demonstrated some alterations in sleep and in memory. In sleep, patients with aMCI spent fewer minutes in slow-wave sleep (SWS) than in the control group, the amount of SWS is smaller in aMCI group than in the control group, theta were reduced during rapid-eye-movement (REM) and both delta and theta were reduced in non-REM sleep in aMCI patients compared with control and, finally, fast spindles counts were reduced in aMCI patients at F3 and F4 recordings sites compared to controls. In memory, recall was better in the control group than in the aMCI group: controls improve their recall in the morning relative to that in the evening whereas aMCI patients did not. Instead, recalling less in the morning compared to the evening. The same occur with recognition [16]. In a study using another method to analyze sleep, the wrist-worn activity sensor, the authors found that, in aMCI group, recognition was better when time in bed was longer and memory decreased when the difficulty in falling asleep increased [15]. However, comparing aMCI patients and controls the actigraphy parameters failed to reveal significant differences. Other study using actigraphy in subjects with naMCI, prove that greater number of wake arousals during the rest interval were significantly associated with poorer nonverbal learning even after controlling for age. The greater duration of wake after sleep onset (WASO) were significantly related to poorer performance on tests of attention, response inhibition and concept forming/problem solving [14]. This article do not included control group.

4. Discussion

Anciently, we believe that sleep was just a passive process in which the body only rested. Nearly the 50' decade, the sleep began to be seeing as a part of the circadian rhythms. While we sleep, several centers and organic systems that inhibit and/or activate important functions are working to provide and regulate the sleep-wake cycle, core body temperature and hormone secretion. The most important endogenous pacemaker that regulates the sleep-wake cycle (and other circadian rhythms) is the hypothalamic suprachiasmatic nucleus. This nucleus receives daylight stimuli from retina and sends stimuli to the pineal which is responsible for melatonin production. The melatonin exercises a synchronization effect at circadian rhythms and can also promote sleep [21]. With aging, the suprachiasmatic nucleus may deteriorate and light exposure may decrease, also decreasing the melatonin production and leading to the disruption of circadian rhythms. The aftermaths of this disruption is a change in sleep in elderly and, more pronounced, in AD patients, in which the alterations in cerebral structure are greater. The most common changes are decrease in sleep time efficient,

greater sleep fragmentation, with more frequent and longer periods of WASO, increase in naps, decreased levels of SWS tendency to go sleep and wake up earlier [22].

The AD is associated with the multiple neurotransmitter systems dysfunction including cholinergic, noradrenergic and serotonergic systems, which also are part of the sleep-wake system [23]. The cholinergic system is involved with a large number of behaviors that are changed in severe AD as attention, learning and memory as well as in sleep-wake cycle [24]. The cholinergic pathways from basal nucleus to the cortex along with the cholinergic pathways from brainstem to the thalamus are involved with the wake promotion and maintenance, as part of the ascending reticular activating system [25,26]. Thus, is probable that the impairment at cholinergic pathways results in an improve in daytime sleepiness already in the early stages of AD [27] and maybe in the MCI subjects. In addition, there are some studies that suggest the redistribution of memory to prefrontal cortex during sleep for memory consolidation [28,29]. Therefore, prefrontal dysfunction found in AD and aMCI may also be relevant for consolidation [30,31].

Recently the sleep spindles that appear on stage 2 sleep are also implicated in memory consolidation. It may possible because the sleep-related memory consolidation is supposed to occur through a dialogue between the hippocampus and neocortical areas, in which sleep spindles appear to play an important role [32]. An study performed with polysomnography compared 14 healthy elderly subjects with 14 AD patients and conclude that a more pronounced fast spindles decrease became evident in AD patients compared to old controls [33].

In the population situated between normal ageing and dementia, people with MCI, we expect to find some alterations. Several studies try to prove this theory. The studies demonstrated that sleep disturbances are prevalent in MCI patients, regardless of type of study (cross-sectional or longitudinal), the criteria for MCI (Petersen criteria or DSM-4) or the tool used (inventory, actigraphy and polysomnographic). In studies that quantified this prevalence, its range about 8.8% [5] until 45.5% [7]. Comparing to subjects without cognitive impairment that have a prevalence between 10.9 [4] and 23.3% and to patients with AD that prevalence of sleep problems, in the literature, can reach 54% [34]. The MCI patients are in the middle, as we might expect in this transitional state. The differences between prevalence maybe is due to the differences in criteria used to MCI, the chosen sample, the follow-up period and the type of study, if cross-section or longitudinal. The second point is the relevance of the sleep problems. At the previous analyze studies, sleep problems appears as being 1 of the 4 most common neuropsychiatric symptoms and were often clinically significant, may result in the need for institutionalization. So it is important to recognize the sleep problems in this population.

Despite the prevalence of sleep disturbs be set between elderly individuals without cognitive impairment and dementia patients, the progression of MCI subjects with sleep problems to dementia is still undefined. A longitudinal study that accompanied MCI patients for 10 years conclude, as a major finding, that sleeping problems were associated with decrease risk for AD [6]. The authors report that this finding is in contrast with the literature and justified the differences

compared to other studies for basically three reasons: the results can vary if it is conducted in a community or in a clinical setting, may depend on the type of rating scale used and the variability may have resulted from an interaction between age, MCI type, the length of the follow-up period, setting, vascular risk factors and diagnostic instruments. Another data also concluded that sleep disturbances alone was not significantly different between MCI patients who remained stable and those who progressed to AD after 25 months on average [35]. On the other hand, two studies demonstrated that the presence of sleep problems in healthy older adults was associated with the incidence of cognitive decline or dementia [36,37] and another ones identified the relationship between this two condition, as we describe hereafter.

To further investigate, some authors analyze the sleep, using actigraphy or polysomnographic, to better understanding what occurs during the MCI patients sleep. In normal aging, there are some changes in the sleep structure as poor sleep efficiency, fragmented sleep, increased in frequency of daytime napping, propensity in fall asleep and wake up earlier and decreased levels of SWS [38,39]. In AD patients, there are the same alterations but in higher intensity [40]. MCI is classified as a transitional stage between normal aging and dementia, then we expected that these patients present the same alterations described in an intermediate intensity. A study that submitted aMCI patients into polysomnographic demonstrated that SWS is dramatically reduced in aMCI, together with borderline changes in REM, REM latency, WASO, sleep efficiency, lower delta and theta power during sleep and reduced stage-2 spindle counts at frontal recording sites [16]. The authors speculate that SWS begins to decline in healthy aging and then declines further in aMCI and DA, whereas in advanced stages of AD, REM decline accelerates such that SWS. A study using an actigraphy in 15 MCI patients also showed a fragmented sleep and poor sleep efficiency, as described in the literature [14]. Despite this results, when MCI patients were compared with healthy elderly controls, a study also using actigraphy parameters, failed to reveal significant differences between the groups, although they observed a trend for phase-delayed in aMCI subjects [15]. This fact possibly occur because the small number of participants (ten aMCI patients and ten controls).

These three studies described above that analyze the presence of changes in the sleep patterns also analyze the relationships between sleep and memory and reached interesting results [14-16]. The data that used the polysomnographic recruited 16 cognitively healthy older adults and 8 aMCI patients and submitted the both groups to 2 declarative memory tests (word-pair recall, fact recognition) and 1 non-declarative memory test (object priming) at night before the register and repeated the tests in the morning after polysomnographic. After 1 week the subjects was submitted to the same protocol. They found that controls improved their recall in the morning relative to that in the evening whereas aMCI patients did not. The same occur with recognition. They conclude that these difficulties in memory processes during sleep are due to the reduction in delta/theta power, which are associated with many types of memory, especially declarative memory that was assessed before sleep, consistent with

the speculation that poor sleep contributes to poor memory in MCI [16]. At the actigraphy studies, the authors cannot explore the delta/theta power but they observed that better sleep predicted better memory and when difficult in falling asleep increased, memory decrease. Participants who exhibited greater across-night sleep variability showed lower story-recall during the neuropsychological battery [15]. In another study, the authors recruited 15 older adults that meet criteria for naMCI and submitted them to a neuropsychological test battery followed by the use of an actigraphy for 14 nights. The results of the battery tests and the actigraphy register were related and converged to two important conclusion: greater number of WASO were significantly associated with poorer nonverbal learning, as well as concept for formation/problem solving and greater durations of WASO were significantly related to poorer performance on tests of attention, response inhibition and concept formation/problem solving [14].

The studies that were described emphasize the presence of a-MCI and DA. But when we talk about MCI and sleep disorders, there is another group which must be cited. Rapid eye movement (REM) sleep behavior disorder (RBD) is a form of parasomnia characterized by the presence of abnormal and often violent motor manifestations during REM sleep [41]. This abnormal behavior result from disorder of the deep nuclei and brainstem neurons involved in the integration of the sleep-wake cycle and the locomotor system [21]. A lot of researches found a link between RBD and synucleinopathies such as Parkinson disease (PD), Lewy body dementia (LBD) and multiple system atrophy [41,42] and are even considered to be early marker for these diseases [43]. In the consensus criteria for LBD, RBD are considered to be suggestive features of the disease [44]. Besides, a study that analyzes the presence of MCI in patients with PD and RBD show that prevalence of MCI in PD with RBD is 73%. In patients with idiopathic RBD the prevalence is 50%, and in PD patients without RBD this proportion decrease to 11%, nearly the same as control subjects (8%) [45]. With this results, they suggest that the presence of RBD is a major risk factor for MCI. Among the subtypes of MCI, the naMCI single domain and aMCI multiple domain were most associated with PD patients with RBD, both characterized by a predominant impairment of executive functions and attention. When Petersen described the MCI criteria, this etiology was already presumed [3].

The analyzed studies do not mention another important issue: the obstructive sleep apnea (OSA). This condition can leads to cognitive deficits mainly in memory and executive functions [46-48]. While OSA does not cause dementia, it could be considered to cause MCI. The patients with OSA is a vulnerable patient due to the entire "package" of daytime somnolence, disordered sleep, subclinical (or clinical) cerebrovascular and cardiovascular disease. So by the possibility of mimics a neurodegenerative disorder and is potentially reversible with treatment, this condition must be investigated and treated in subjects with decline in cognitive functions. Furthermore the e4 allele of apolipoprotein E (APOE), which is a major risk factor for AD [49], has been associated with OSA in adults especially in the setting of cognitive problems [50]. OSA is itself detrimental for cognition, especially among those at greater risk for AD due to their APOE e4 carrier status.

Finally, both patients with cognitive impairment may have sleep problems, because of the pathway neurodegeneration common to the two functions, as patients with sleep problems may develop cognitive impairment, because the dysfunction that sleep disturbance cause in memory consolidation.

5. Conclusion

Summarizing, sleep disturbance is prevalent and can be predictive of cognitive decline in older people and in those with neurodegenerative disorders. The sleep problems have to be identified and treat to preserve the cognition and the MCI subjects with sleep disturbances have to be follow more closely to identify the initial signs of dementia.

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