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Estudo de revisão

How sleep disorders affect patients with Alzheimer's disease

Como os distúrbios do sono afetam pacientes com doença de Alzheimer

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Abtract: Sleep disorders are common in patients with Alzheimer's disease. These disorders are highly related to the cognitive impairment and have as main risk factor the time of disease. Additionally, they can damage the patient's quality of life, as well as their family's and caregivers'. The aim of this study was to clarify which changes in sleep patterns occur in patients with Alzheimer's disease and how they occur. This narrative literature review was performed using five databases: MEDLINE, LILACS, Web of Science, Scopus, and Science Direct. Search terms were: Alzheimer's disease, sleep-wake disorders, and dyssomnias. The research included articles published between 2000 and 2018, written in English, Portuguese and Spanish. Results showed that Alzheimer's disease is related mainly to REM sleep alterations, day-time sleepiness and napping, increased sleep fragmentation, and other less frequent disorders, such as decreased sleep efficiency and total sleep time, breathing disorders, and increased motor activity. Deposition of β-amyloid protein is the main pathophysiological substrate of sleep disorders, combined with increased orexin levels due to cholinergic deterioration in the central nervous system, and elevation of serum proinflammatory cytokines, associating circadian alterations with neuroinflammation. Therefore, sleep disorders are an important comorbidity in Alzheimer's disease, and can present in several ways, impairing the quality of life of these patients. The pathophysiological mechanisms of these comorbidities have not yet been fully elucidated, and further research that seeks to explain all these gaps is warranted.

Key words: Alzheimer disease. Neurodegenerative disease. Sleep disorders. Dyssomnias.

Resumo: Os distúrbios do sono são comuns em pacientes com Doença de Alzheimer. Esses distúrbios estão altamente relacionados ao comprometimento cognitivo e têm como principal fator de risco o tempo da doença. Além disso, eles podem prejudicar a qualidade de vida do paciente e de seus familiares e cuidadores. O objetivo deste estudo foi esclarecer quais alterações nos padrões de sono ocorrem em pacientes com doença de Alzheimer e como elas ocorrem. Esta revisão narrativa da literatura utilizou cinco bases de dados: MEDLINE, LILACS, Web of Science, Scopus e Science Direct. Os termos de pesquisa foram: doença de Alzheimer, transtornos do sono e vigília e dissonias. Foram incluídos artigos publicados entre 2000 e 2018, escritos em inglês, português e espanhol. Os resultados mostraram que a doença de Alzheimer está relacionada, principalmente, a alterações do sono REM, sonolência e cochilos diurnos, aumento da fragmentação do sono, além de diminuição da eficiência do sono e do tempo total de sono, distúrbios respiratórios e aumento da atividade motora. A deposição de proteína β-amilóide é o principal componente dos distúrbios do sono, combinada ao aumento dos níveis de orexina pela deterioração colinérgica no sistema nervoso central e elevação das citocinas pró-inflamatórias séricas, associando alterações circadianas à neuroinflamação. Portanto, os distúrbios do sono são uma comorbidade importante no Alzheimer e podem se apresentar de várias formas, prejudicando a qualidade de vida desses pacientes. Os mecanismos desses distúrbios ainda não foram totalmente elucidados, e necessitam de mais pesquisas que busquem explicar todas essas lacunas.

Palavras-chave: Doença de Alzheimer. Doença neurodegenerative. Transtornos do sono-vigília. Dissonias.

INTRODUCTION

Sleep disorders are often present in the various types of dementia and progress in an age-dependent manner. The association of these disorders with Alzheimer's disease (AD) is widely described in the literature, but their pathophysiological mechanisms are not yet fully elucidated, even though a broad spectrum of clinical manifestations can be observed (CHWISZCZUK et al., 2016; JYOTI et al., 2015).

In AD, changes in the sleep pattern have a strong association with cognitive impairment. Variables involved in the context of sleep disorders, such as the increase of waking hours, are directly associated with low scores in the Mini-Mental State Examination (MMSE), one of the tests used for cognitive assessment of these patients, based on the evaluation of several superior cortical functions. In AD, the frequency of day-time napping can directly affect the course of the disease (LIGUORI et al., 2016; OHADINIA et al., 2004; TRACTENBERG et al., 2005; VOLICER et al., 2001).

Some hypotheses seek to explain the development of sleep disorders in AD. Increased levels of orexin, a neuropeptide with a role in sleep regulation, could determine wakefulness levels, and have been observed in AD patients, showing association with sleep fragmentation and alterations in rapid eye movement (REM) sleep in this population. The

relationship between elevated serum TNF-α levels and the occurrence of day-time sleepiness in patients with mild to moderate AD has also been demonstrated (CHEN et al., 2012; LIGUORI et al., 2016).

Low socioeconomic status and some psychiatric disorders found in patients with AD may be associated with the change in the sleep patterns of these individuals. There is evidence that sleep-maintenance insomnia, i.e., multiple awakenings during the night, can lead to paranoid delusions, aggressions, and anxiety (CAMARGOS et al., 2011; OWNBY et al., 2014; TRACTENBERG et al., 2005).

Due to the high occurrence of sleep disorders in patients with AD, which directly affects the quality of life of the patients and of their caregivers (CHWISZCZUK et al., 2016), there is a need for studies that can bring some clarification on this issue and prompt relevant discussions on the subject. In this study, through a literature review, we analyzed the main types of sleep disorders related to AD and explained the pathophysiological mechanisms of these disorders.

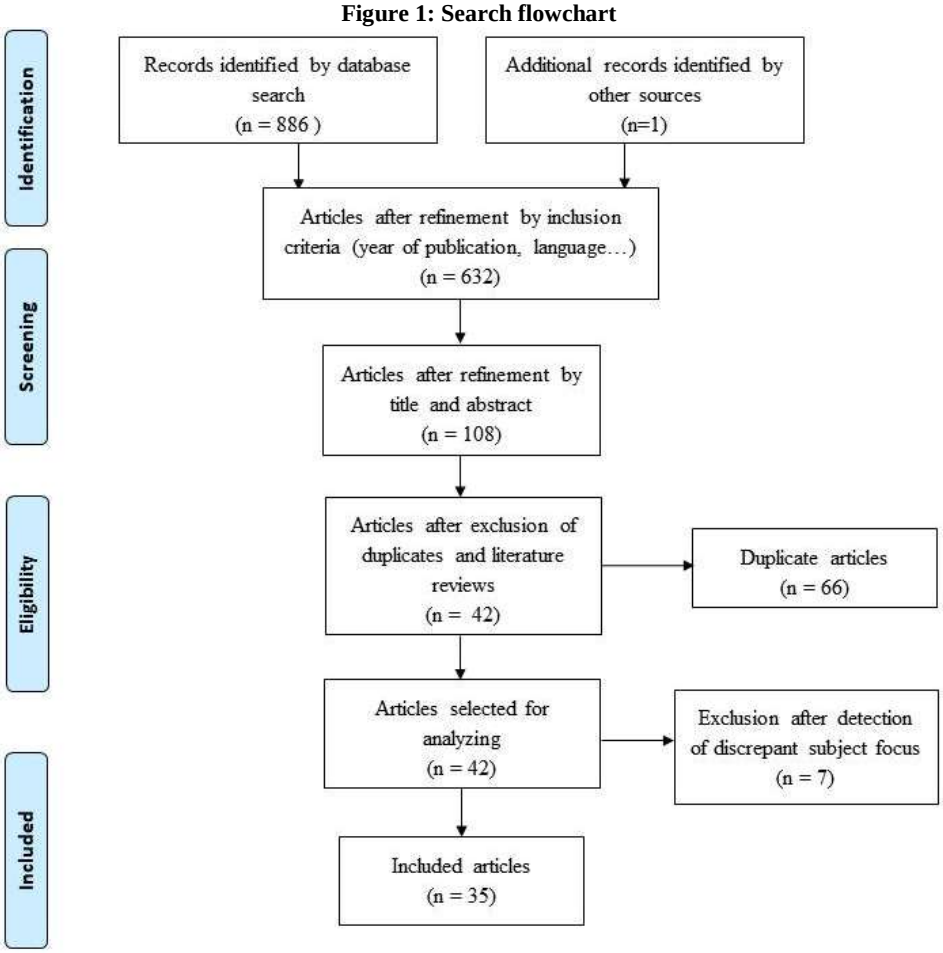
METHODS

A literature review was carried out through search of scientific articles using the following search terms: "Alzheimer's disease", "sleep-wake disorders", and "dyssomnias". The combinations of search terms were: "Alzheimer's disease" AND "sleep-wake disorders", and "Alzheimer's disease" AND "dyssomnias". We used five databases: MEDLINE, LILACS, Web of Science, Scopus, and Science Direct, with two of the researchers selecting the articles and the search yielded 886 records. Some different data were added using other basis.

Inclusion criteria were: original articles on neurodegenerative disease-related sleep disorders, specifically Alzheimer's disease, published between the years 2000 and 2018 in English, Spanish, and Portuguese. Exclusion criteria were: articles published prior to the year 2000, in languages other than English, Portuguese, and Spanish, and with only the abstract available in the databases. After the screening, 255 articles were excluded and 632 articles remained for analysis and selection.

After the reading of titles and abstracts, 108 articles remained included. After the exclusion of duplicates, there were 42 articles left for full text analysis. After full text reading, seven articles were excluded for having a direction that diverged form our objectives. All these steps are summarized in the flow chart (**Figure 1**) (MOHER et al., 2009).

Figure 1: Search flowchart



RESULTS AND DISCUSSION

Risk factors for the development of sleep-wake disorders (SWD) in patients with AD

The term Sleep-Wake Disorders (SDW) appeared in the context of sleep disorders classification with the goal of emphasize that the disorders found in this group include all 24-hours cycle, not only the sleep interval. Are contemplated in the concept patterns of disturbance in the circadian cycle caused by endogenous misalignment, waking disturbances such as daytime sleepness and insomnia, and, lastly, disturbances associated with functional impairment (SATEIA, 2014). Women present significantly a major representativeness when considered AD and SWD group, as well as advanced age, over 70 years (GUARNIERI et al., 2012), confirming that aging process is described as a risk factor for several types of SWD (CHEN et al., 2012; OLIVEIRA et al., 2014; SHIH et al., 2017) (**Table 1**).

These changes in sleep patterns are even more common in several types of dementia, in which Alzheimer's disease (AD) stands out (CHWISZCZUK et al. 2016). Patients can be affected by sleep disorders even in milder clinical presentations of the disease, in which they present with circadian cycle dysfunctions and changes in the electroencephalogram. The severity of SWD is related to the evolution of the disease (JU et al., 2013; PARK et al., 2011).

Table 1: Risk characteristics according to each author

Risk factors to the development of SWD in AD patients	Authors
Women	GUARNIERI et al., 2012
Aging	SHIH et al., 2017; OLIVEIRA et al., 2014; CHEN et al., 2012
Scholarity	OLIVEIRA et al., 2014; CAMARGOS et al. 2011.
Duration of Disease	PARK et al., 2011; JU et al., 2013; CAMARGOS et al. 2011; YESAVAGE et al, 2002; GARCÍA-ALBERCA et al., 2013;
Severity of Disease	CAMARGOS et al. 2011; MORAN et al. 2005; CHWISZCZUK et al., 2016;

The duration of disease has been reported as a risk factor for the development of sleep disorders in patients with AD. Most patients are affected by sleep disorders after the fourth year of disease, and the frequency of day-time napping increases over time (GARCÍA-ALBERCA et al., 2013; JU et al., 2013; OHADINIA et al., 2004; YESAVAGE et al., 2002). Aging alone does not directly interfere with sleep, even though it can make individuals more susceptible to factors that cause sleep alterations. Therefore, there is a direct correlation between sleep disorders and AD (PEREIRA; CEOLIM, 2011).

The level of education of patients with AD is also associated with insomnia (CAMARGOS et al., 2011; OLIVEIRA et al., 2014). Insomnia is associated with low level of education, low income, divorce, and widowhood even in populations not affected by AD (CRUZ et al., 2009).

Types of SWD present in patients with AD

Observing the circadian rhythm of patients with AD in comparative studies with control groups, it can be said that AD has a correlation with various sleep disorders (GAGNON et al., 2006). The AD-related sleep disorders most frequently reported in the literature are REM sleep disorders, excessive day-time sleepiness, day-time napping, and increased sleep fragmentation.

In patients with AD there is a decrease in total sleep time and in sleep efficiency, in addition to fewer REM sleep periods and increased sleep latency (ISMAIL et al., 2009; OLIVEIRA et al., 2014). REM sleep without atony, which is included in REM sleep disorders, has a direct association with synucleinopathies, characteristic of neurodegenerative disorders (GAGNON et al., 2006; MAESTRI et al., 2015). There is, therefore, a decrease in the depth of sleep, which can be demonstrated by increased waking hours in patients with AD, who spend more time awake in bed (MOST et al., 2012).

AD is also correlated with excessive day-time sleepiness and day-time napping (TRACTENBERG et al., 2003; TRACTENBERG et al., 2005). These symptoms can be present even in mild to moderate stages of the disease, even though SWD are related to the cognitive impairment of neurodegeneration. There is also association of excessive day-time sleepiness with obstructive sleep apnea and increased sleep fragmentation (BONAKIS et al., 2014; OHADINIA et al., 2004). Day-time sleepiness also leads to increased wake-up time after sleep onset and decreased slow-wave sleep duration (CHEN et al., 2012; COLBY-MILLEY et al., 2015; HITA-YAÑES et al., 2013; TRACTENBERG et al., 2006). There is also the occurrence of day-time behavioral disorders, such as day-time agitation, consequence of multiple awakenings at night and sleep-disordered breathing, such as loud snoring and irregular breathing, contrasted with decreased motor activity, in addition to the need for hypnotic and benzodiazepine medications for sleep satisfaction, as there is increased

motor activity at night (MORAN et al., 2005; TRACTENBERG et al., 2005; TRACTENBERG et al., 2006; VOLICER et al., 2001; YOU, et al., 2015).

Advanced AD is associated with a disorder described as sundown syndrome, characterized by behavioral disorders in the evening and a break in the circadian rhythm. The break occurs because the accumulation of β-amyloid protein affects brain regions responsible for the sleep-wake cycle. This makes AD a risk factor for the development of the syndrome. The syndrome is characterized mainly by sleep fragmentation, longer and more periods of nocturnal activity, waking up at night thinking it is day-time, and staying awake at night (JU et al., 2013). The quality of sleep, when improved, also improves the syndrome, since they have a positive correlation with each other (SHIH et al., 2017). A positive association of physical activity practice with the clinical improvement of the syndrome was observed (JU et al., 2013; MINAKAWA et al., 2017).

All of these changes in the sleep pattern can be observed in the study with transgenic animals. PLB1 triple (gene modified for AD) mice also have increased total wakefulness and reduced non-REM sleep and REM sleep. This corroborates how often these changes are found in the articles reviewed. Changes in electroencephalogram patterns as of the sixth month of life of the animals, with age-related progression, are also found. There is an increase in wakefulness over the months, in addition to an overall decrease in sleep. Genetic modification for AD led to the occurrence of SWD at 13, 17, and 21 months, compared to non-genetically modified animals, showing the acceleration of the sleep degeneration process associated to the gene for AD (JYOTI et al., 2015). There is evidence in humans to support the idea that even though sleep is affected by AD, there is a worsening of sleep quality, especially in those with a genetic predisposition to sleep disorders (YESAVAGE et al., 2002).

Etiology of SWD in patients with AD

In the various types of dementia, sleep disorders are probably of central etiology, as a consequence of neurodegeneration itself. Involvement of the frontal cortex would, for example, lead to non-REM sleep dysregulation. Neurodegeneration can progress due to sleep alterations, since slow-wave sleep is critical in restoring the prefrontal cortex (BONAKIS et al., 2014). The reduction of sleep quality due to circadian dysregulation has been emerging as a theory for the increase of β-amyloid deposition from the beginning of the disease, being responsible for the endless cycle of disease progression and sleep degeneration (LIGUORI et al., 2016) (**Table 2**).

Table 2: Sleep disorders in AD according to each author

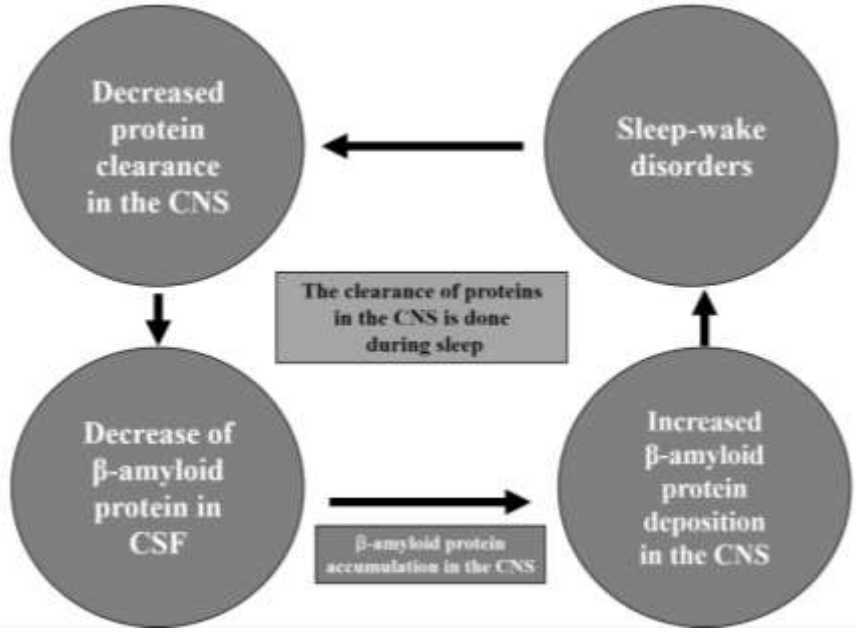
Types of SWD in AD	**Authors**
Decrease in sleep total duration	GAGNON et al, 2006; CHEN et al., 2012; MINAKAWAA et al., 2017;
Decrease in sleep efficiency	GAGNON et al, 2006; CHEN et al., 2012; JU et al., 2013; MINAKAWAA et al., 2017; TRACTENBERG, 2005; LIGUORI et al., 2014
REM sleep Disturbances	GAGNON et al, 2006; BONAKIS et al., 2014; MAESTRI et al., 2015; LIGUORI et al., 2016; CHEN et al., 2012; YIN et al., 2016; PASE et al., 2017; MOST et al., 2012; JYOTI et al., 2015; LIGUORI et al., 2014; OLIVEIRA et al., 2014; ISMAIL et al., 2009; COLBY-MILEY et al., 2015; HITA-YAÑES et al., 2012;
Increase in REM sleep latency	GAGNON et al, 2006; BONAKIS et al., 2014; LIGUORI et al., 2016; YIN et al., 2016; PASE et al., 2017; LIGUORI et al., 2014
Increase in wakeness total duration	BOKENBERGER et al., 2017; MOST et al., 2012; JYOTI et al., 2015; TRACTENBERG, 2005; COLBY-MILEY et al., 2015;
Excessive day-time sleepiness and day-time napping	BONAKIS et al., 2014; CHEN et al., 2012; JU et al., 2013; YIN et al., 2016; PARK et al., 2011; MOST et al., 2012; OWNBY et al., 2014; JYOTI et al., 2015; TRACTENBERG, 2006; OHADINIA et al. 2004; TRACTENBERG, 2003; TRACTENBERG, 2005; JU et al., 2013;
Increase of sleep fragmentation	BONAKIS et al., 2014; LIGUORI et al., 2016; CHEN et al., 2012; JU et al., 2013; MINAKAWAA et al., 2017; MORAN et al., 2005; MOST et al., 2012; OWNBY et al., 2014; JYOTI et al., 2015; TRACTENBERG, 2006; OLIVEIRA et al., 2014; TRACTENBERG, 2005
Decrease of non-REM sleep	MAESTRI et al., 2015; CHEN et al., 2012; JYOTI et al., 2015; LIGUORI et al., 2014; ISMAIL et al., 2009; COLBY-MILEY et al., 2015; HITA-YANES et al., 2012
Day-time agitation	MORAN et al., 2005
Respiratory Sleep Disorders	BONAKIS et al., 2014; CAMARGOS et al., 2011; JU et al., 2013; TRACTENBERG, 2006; TRACTENBERG, 2005
Increase of night-time motor activity	VOLICER, 2001; ISMAIL et al., 2009

It is suggested that the suprachiasmatic nucleus is one of the anatomic areas of the brain affected by the evolution of Alzheimer's disease. This area is considered as the pacemaker of the sleep-wake cycle, and its dysfunction may be related to the development of sleep disorders in patients with AD (MORAN et al., 2005; VOLICER et al., 2001). The

pathophysiology of AD, based on the deposition of β-amyloid protein, brings consistent pathophysiological substrates to sleep dysregulation in the disease (COLBY-MILLEY et al., 2015; GERSTNER et al., 2017; JU et al., 2013). Mice with fragmented sleep have increased amyloid deposition, and day-time sleep disturbances may increase this protein production or reduce its clearance, aggravating its deposition (BOKENBERGER et al., 2016; MINAKAWA et al., 2017). Accumulation of β-amyloid plaques in the hippocampus of mouse models showed sleep fragmentation after plaque formation. In addition, low levels of this protein in cerebrospinal fluid, suggestive of deposition, maintain a positive relationship with poor sleep quality and increased wake-up time after sleep onset. Increased frequency of day-time napping per week is also related to the levels of β-amyloid deposition. As the neurodegeneration progresses, day-time naps become more frequent and sleep quality further deteriorates (JU et al., 2013; MINAKAWA et al., 2017).

The clearance of β-amyloid in the central nervous system is performed by elements of neuroglia such as microglia and astrocytes, which drain these types of peptides into the perivascular spaces. This process is compromised in AD, in which the drainage into the subarachnoid space becomes inefficient (TORRES et al., 2012). Non-clearance of various types of protein leads to abnormal protein accumulation and subsequent neuronal loss, inducing disorders according to the affected central nervous system area. The deposition of tau protein, also involved in AD pathophysiology, points to interferences in the regulation of the sleep-wake cycle, due to the deposition in key areas in the control of circadian mechanisms. Sleep disorders, in turn, would be involved in decreasing the elimination of these proteins, mainly of the β-amyloid protein, but also of the tau protein, since this clearance mainly occurs during sleep, leading to progression of accumulation (BURKE et al., 2016; LIGUORI et al., 2014), as shown in **Figure 2**.

Figure 2: Cicle of β-amyloid protein deposition in sleep disorders. CNS: central nervous system. CSF: cerebrospinal fluid

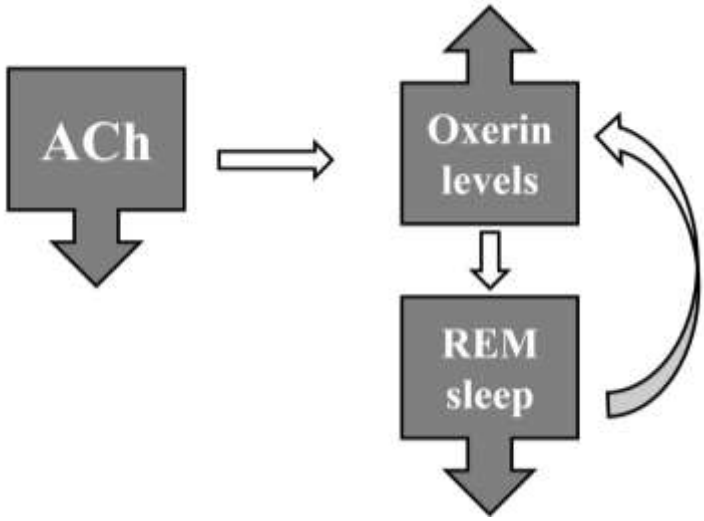


Genetics also appears to play an important role in sleep disorders in patients with AD. ApoE is a protein produced in several places in the human body. The brain is the second largest production site, thanks mainly to astrocytes and microglia. The synthesis of ApoE is increased in processes of neurodegeneration in order to compensate these processes, participating in the formation of senile plaques and neurofibrillary tangles in AD (OJOPI et al., 2004). Positive ApoE e4 genotypes and the lower expression of genotypes including ApoE e3, which are genes involved in the increased risk of AD, lead to the presence of a greater amount of circulating ApoE, and appear to be related to sleep disorders in these patients (BURKE et al., 2016; OJOPI et al., 2004). The presence of these genotypes is associated mainly with increased sleep fragmentation and decreased REM sleep; even though they can appear in advanced stages of the disease, they mainly appear in the earlier stages of the clinical course of dementia (OLIVEIRA et al., 2014).

In the stages of cognitive impairment of AD, the participation of the orexin system deterioration is suggested. This neuropeptide, produced by hypothalamic neurons, would play a role in the maintenance of wakefulness by increasing excitation; therefore, it would play a role in regulating the sleep-wake cycle. There is a low orexin tonus during REM sleep, and increased levels of orexin appear to correlate with the suppression of this sleep phase, which would lead to REM sleep disorders (LIGUORI et al., 2016). In addition, sleep deprivation also increases orexin levels, which would maximize these disorders (OJOPI et al., 2004).

Increased orexin levels are already present in the mild cognitive impairment (MCI) phase, and are associated with the appearance of insomnia, increased sleep latency, and multiple night awakenings. The occurrence of these SWD before the consolidation of dementia is the first sign of sleep impairment in AD. However, this correlation is more significant in severe AD, in which patients have significantly higher levels of orexin in cerebrospinal fluid. These levels are directly linked to increased sleep latency, decreased sleep efficiency, and decreased REM sleep (LIGUORI et al., 2014). The degeneration of cholinergic projections in the basal forebrain, as well as neurotransmitter release disorders, are consolidated in the pathophysiology of circadian dysregulation in AD, and bring the change in cholinergic transmission as a factor in the positive orexin balance, overexpressing its levels, which would justify the increase in wakefulness, according to **Figure 3 (**LIGUORI et al., 2016; PASE et al., 2017).

Figure 3: The Acetylcholine (Ach) déficit incerases the orexinergic tone, influencing the decrease in REM (rapid eye moviment) sleep. In turn, REM sleep deprivation increases orexin levels, maximizing the sleep disorder.



A strong influence of neuroinflammation may also be involved in the process of sleep deterioration. Pro-inflammatory cytokines, such as IL-1β and TNF-α, with local production and activation in the central nervous system appear to be significantly increased in individuals with AD compared to healthy elderly. Significant differences in serum TNF-α were positively correlated with the occurrence of excessive day-time sleepiness in patients with AD (CHEN et al., 2012). IL-1β also decreases REM sleep in mice as well as in patients with AD with genetic polymorphisms for IL-1β overexpression, besides inducing non-REM sleep and being responsible for sleep deprivation symptoms such as fatigue and cognitive decline. IL-1β levels have also been shown to be related to increased occurrence of day-time sleepiness, decreased sleep efficiency at night, and increased REM sleep latency. Furthermore, when associated with genotypes positive for ApoE e4 gene, there is a synergistic effect on the overexpression of inflammatory cytokines and worsening of these sleep disorders (YIN et al., 2016).

The pathophysiological mechanisms described above and their frequency distribution according to the literature are shown in **Table 3**.

Table 3: List of articles that cite pathophysiological mechanisms of sleep disorders in patients with AD

Pathophysiologic mechanisms involved in sleep disturbances in AD	**Authors**
Plaques of β-amiloid protein e low LCR levels	COLBY-MILEY et al., 2015; GERSTNER et al., 2016; JU et al., 2013; MINAKAWAA et al., 2017; BOKENBERGER et al., 2017; LIGUORI et al., 2014;
Interference of gene likes APOE	BURKE et al. 2016; OLIVEIRA et al., 2014; HITA-YANES et al., 2012; YIN et al., 2016
Deterioration of orexinergic system	LIGUORI et al., 2016; PEDRAZZOLI et al., 2004; MORAN et al., 2005; LIGUORI et al., 2014; OLIVEIRA et al., 2014;
Cholinergic disregulation	LIGUORI et al., 2016; PASE et al., 2017; LIGUORI et al., 2014; OLIVEIRA et al., 2014;
Cytokines (IL-1β and TNF-α)	CHEN et al., 2012; YIN et al., 2016;

Factors associated with sleep disorders in patients with AD

Alzheimer's disease patients, in association with SWD, present a superior trend of aggressiveness. In patients with AD, a greater occurrence of aggressive events in association with sleep-disordered breathing, such as sleep apnea and snores was observed. These events manifest in the form of movements, verbal agitation, aggressive behaviors, and physical threats. The presence of sleep disorders was also associated with cognitive dysfunctions, psychological disorders, and behavioral disorders (BOKENBERGER et al., 2016; CAMARGOS et al., 2011; CHWISZCZUK et al. 2016; JU et al., 2013; MORAN et al., 2005).

The onset of other psychiatric disorders in patients with AD is also associated with the occurrence of sleep disorders. Insomnia can be one of the signs of depression or anxiety, which greatly affect patients with AD. Depressed mood is strongly associated with sleep alterations, and depression predicts an even greater severity of these alterations (JU et al., 2013; MORAN et al., 2005; TRACTENBERG et al., 2006).

Day-time sleepiness has a good relationship with greater cognitive and functional decline in these patients, and subjects with day-time sleepiness have a lower MMSE score compared to matched controls. It is also related to elevation of serum IL-1β and TNFα (CHEN et al., 2012; OLIVEIRA et al., 2014). Thus, the severity of dementia is positively related to increased day-time napping, reflecting the existence of these sleep disorders (OHADINIA et al., 2004; VOLICER et al., 2001; YESAVAGE et al., 2002).

Another disorder that is associated with AD is parkinsonism, which is an associated disorder in these patients. Its appearance is a factor of poor prognosis in the evolution of the disease. Parkinsonism in AD is associated with day-time sleepiness and periodic limb movements, causing more awakenings, which aggravates the sleep dysfunctions of these individuals (PARK et al., 2011).

CONCLUSION

Studies have shown that sleep disorders very often are part of AD clinical picture, relating to the evolution of the disease. REM sleep disorders, excessive day-time sleepiness and day-time napping, and increased sleep fragmentation are the most common manifestations.

The pathophysiology of sleep disorders in patients with AD appears to consist of increased orexin levels due to cholinergic dysregulation and increased IL-1β and TNFα in the central nervous system. The disease also affects sleep-regulating brain areas by the deposition of β-amyloid protein.

However, due to the lack of knowledge on this area, studies that address this issue, taking into account the impact of these disorders on the daily life and quality of life of millions of people with AD, are warranted.

LIMITATIONS

The inclusion of articles according to language (English, Portuguese and Spanish) is certainly a limitation in our study, once were excluded articles in French and German that could have important information to be added. Another limitation was the duration of compilation of works, being possible the exclusion of newer studies that could add relevant discoveries about the subject.

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ABBREVIATION

AD – Alzheimer’s disease
MMSE – Mini-Mental State Examination
MCI – mild cognitive impairment
REM – rapid eye movement
SWD – sleep-wake disorders

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