

# Incidence of sleep disorders in patients with Alzheimer disease

## Incidência de distúrbios do sono em pacientes com doença de Alzheimer

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### ABSTRACT

**Objective:** To determine the incidence of sleep disorder at a follow-up examination from 1 to 4 years, in demented patients diagnosed at first visit, besides analyzing associated demographic and comorbidities characteristics. **Methods:** A total of 122 elderly patients aged 60 years or older and diagnosed with dementia (Alzheimer and other) were followed in a reference geriatric center for dementia. The clinical protocols included interviews with patient and caregiver, complete physical examination, laboratory and imaging tests. Criteria for the diagnosis of sleep disorder included complain of insomnia from the patient or caregiver using the Neuropsychiatric Inventory nighttime. **Results:** The incidence density of sleep disorder among demented was 18.7/100 person/years. The risk of developing sleep disorder within the first and fourth years of follow-up was 9.8% and 50.9%, respectively. Multivariate Cox regression analysis revealed that educational level less than 8 years and report of aggressiveness at baseline were an independent predictor of sleep disorder, increased risk in 3.1 (95%CI: 1.30-9.22) and 2.1 times (95%CI: 1.16-4.17), respectively. **Conclusion:** The incidence of sleep disorder in demented patients was elevated, and was particularly associated to low educational level and aggressiveness at admission.

**Keywords:** Sleep disorders; Aged; Dementia; Alzheimer disease; Sleep initiation and maintenance disorders

### RESUMO

**Objetivo:** Determinar a incidência de distúrbios do sono em seguimento de 1 a 4 anos em pacientes com demência diagnosticada na primeira consulta, além de analisar características demográficas e comorbidades associadas. **Métodos:** Cento e vinte e dois idosos com 60 anos ou mais e com o diagnóstico de demência (Alzheimer e outras) foram seguidos em um centro de referência geriátrico para demência. O protocolo clínico incluiu entrevista com o paciente e o cuidador, exame físico, laboratorial e de imagem. Os critérios para diagnóstico dos distúrbios do sono incluíram queixa de insônia pelo paciente ou cuidador utilizando o item sobre comportamentos

noturnos do Inventário Neuropsiquiátrico. **Resultados:** A densidade de incidência de distúrbios do sono foi de 18,7/100 pessoas/ano. O risco de desenvolver distúrbios do sono no primeiro e quarto anos de seguimento foi de 9,8% e 50,9%, respectivamente. Análise multivariada de Cox revelou que o nível educacional menor que 8 anos e a presença de agressividade na primeira consulta foram fatores preditores independentes para desenvolver distúrbios do sono no seguimento, aumentando o risco em 3,1 (IC95%: 1,30-9,22) e 2,1 (IC95%: 1,16-4,17) vezes, respectivamente. **Conclusão:** A incidência de distúrbios do sono em pacientes dementes foi elevada e, neste estudo, particularmente associada ao baixo nível educacional e à agressividade na admissão.

**Descritores:** Distúrbios do sono; Idoso; Demência; Doença de Alzheimer; Distúrbios do início e da manutenção do sono

### INTRODUCTION

Sleep disorders (SD) have a large impact on the life of patients with dementia and their caregivers. SD increase the risk of institutionalization<sup>(1)</sup>, worsen the severity of Alzheimer disease (AD)<sup>(2)</sup> and affect the health of caregivers<sup>(3)</sup>.

SD are very common in AD<sup>(4,5)</sup>. Populational studies have identified prevalence of up to 40% in many AD stages<sup>(4,6)</sup>. However, to our knowledge, no studies have examined incidence of SD in a follow-up period of AD and other demented patients.

### OBJECTIVE

To evaluate the incidence of SD in a cohort of Brazilian patients with AD and other dementias after a 4-year follow-up period, and to identify the risk factors associated with it.

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Conflict of interest: none

## METHODS

This is a retrospective cohort study approved by the Ethics Research Committee of Universidade de Brasília (UnB), CEP FM-UnB 080/2005.

### Participants

We included patients diagnosed with dementia, followed for at least 12 months, during which time they were examined at least twice. The visits to each patient during 2008 and the records from these visits in the previous years since their first visit were considered.

Among the 250 patients followed in the Geriatric Medical Centre in 2008 (Cognitive Geriatric Unit), 128 were excluded because they were followed up for less than 1 year (n = 39), had mild cognitive impairment (n = 20), and other possible causes of cognitive impairment (depression, hypothyroidism, syphilis, use of medication or alcohol intake).

At admission, 31.4% (56/178) of patients already presented SD. Therefore, we selected for analysis 122 patients with dementia and without SD at baseline. Baseline characteristics are summarized in table 1. The Centre where analysis was done is accredited by the Brazilian Ministry of Health as a reference center for patients with AD.

**Table 1.** Baseline characteristics of subjects without sleep disorders (n = 122) at baseline

Characteristics	Number of patients	Proportion (%)
Gender		
Women	76	62.3
Men	46	37.7
Educational level in years		
Illiterate	19	15.5
Less than 4 years	54	44.3
Between 4 and 8 years	26	21.3
More than 8 years	23	18.9
Functionality		
Dependent	94	77
Independent	28	23
Types of dementia		
Alzheimer disease	76	62.3
Mixed	16	13.1
Vascular dementia	7	5.7
Frontotemporal dementia	7	5.7
Lewy body dementia	6	4.9
Other	10	8.3
CDR		
1	53	43.4
2	57	46.8
3	12	9.8

CDR: Clinical Dementia Rating.

### Assessment

Demographic and clinical data collected by interview and evaluation included gender, age, educational level (illiterate; less than 4 years; between 4 and 8 years; more than 8 years), number of drugs used per patient, functionality, type of dementia and misdiagnosis (defined as diagnosis that changed from AD to other dementia or vice-versa during the follow-up period).

Aggressiveness was considered when a positive response to the following questions was given: Does the patient have periods when he/she refused to cooperate or denied help? Are they hard to care for? (aggression/agitation, item C, Nighttime Behavior scale– NPI)<sup>(7)</sup>.

Clinical data was gathered using the Objective Geriatric Assessment, a screening instrument developed for teaching and research in our Centre. Patients had complete physical examinations, laboratory tests and imaging examinations. The criteria used were: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)<sup>(8)</sup> for the diagnosis of dementia; the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA)<sup>(9)</sup> criteria for AD (probable); the Instrumental Activities of Daily Living (IADL) for functionality<sup>(10)</sup>; the Clinical Dementia Rating (CDR) for characterization of demential stage<sup>(11)</sup>; and neuropsychological testing for cognitive assessment.

The NPI scale includes eight items that are rated as to how often they occurred during the past month<sup>(7)</sup>. SD was considered when the following criteria occurred:

- complaint of SD from patient or caregiver<sup>(12)</sup> according to NPI items;
- exhaustion of caregiver (score  $\geq 2$ ; scale from 0 to 5, with 2 indicating mild distress, according to NPI);

The diagnosis of SD was established, according to the above criteria, at baseline and during the follow-up period at each visit.

Polysomnography and actigraphy were not done. Structured sleep diaries were not requested because of the low educational level of the patients or caregivers, and the high proportion of patients with advanced degrees of dementia.

### Data analysis

Incidence density was calculated by dividing the number of SD by the total population-time of follow-up. Incidence density is an appropriate measure to estimate the occurrence rate of various outcomes in a dynamic population<sup>(13)</sup>. Cox proportional hazards

regression were used to determine the risks of SD. Groups of related variables were examined in separate multivariate analyses. Baseline variables were statistically significant at  $p \leq 0.10$  in univariate regression analyses and were included in the construct-specific multivariate Cox models. The independent predictors of SD, significant at  $p \leq 0.05$  for each group of variables, were included in a final overall multivariate model. The statistical package SAS 9.1 was used to perform the statistical analysis (SAS Institute, Inc., Cary, NC).

## RESULTS

At baseline, approximately 2/3 of the patients (62%) were women and the mean age was 78.5 ( $\pm$  7.6) years.

These 122 subjects were followed for 277.9 persons/year. Of these patients, 52 (42.6%) developed SD between the baseline visit and the end of the follow-up. Thus, the incidence density of SD among demented was 18.7/100 person/year. The risk of developing SD between the first and fourth years of follow-up was 9.8% and 50.9%, respectively.

Patients with AD showed the highest rate of SD with 47% (34/76), followed by vascular dementia with 42.8% (3/7) and mixed dementia with 37.5% (6/16).

Less than 8 years of education [hazard ratio (HR): 3.1; 95%CI: 1.30-9.22] and reporting aggressiveness (HR: 2.1; 95%CI: 1.16-4.17) increased the risk of SD. No other variable was predictive of SD at baseline or follow-up.

## DISCUSSION

To our knowledge, this is the first retrospective cohort study of SD in demented patients (AD and other).

The rate of 18.7/100 persons/year that we observed is of concern considering the impact SD can have on demented patients and their caregivers. A 3-year follow-up of elderly people without dementia revealed that 15% who did not report sleep difficulty at baseline had disturbed sleep on follow-up, suggesting an annual incidence rate of approximately 5%<sup>(14)</sup>. Other similar study observed that the early incidence was 2.8%<sup>(15)</sup>.

Other studies observed high prevalence of SD among patients with dementia<sup>(4-6,16,17)</sup>, but our investigation was the first cohort study on SD among demented patients (AD and other). The high incidence of SD may reflect the greater severity of disorders observed in the referral Centre. Although the caregivers of the patients often complained about difficulties in sleep maintenance, it laid beyond the scope of this study to assess the frequency or to categorize the intensity of the patients' SD.

These aspects would be better determined by using polysomnography or actigraphy.

SD or disruption is common among patients experiencing different types of dementia. A recent study in non-institutionalized patients with frontotemporal dementia showed sleep-wake disorders, with reduced sleep efficiency and reduction of total sleep time<sup>(18)</sup>. Grace et al.<sup>(17)</sup> identified poor sleep quality in eight (53%) patients with Lewy body dementia and in three (15%) with AD. Factors that contribute to the large variation in the prevalence of SD in this group of patients may be related to the degree of dementia and to the type of SD assessed. Another important factor complicating SD diagnosis is the association with behavioral disorders and other illnesses often misdiagnosed as dementia.

Aggressiveness is common among these patients<sup>(5)</sup>. Combination of cognitive, functional, and behavioral impairments were associated with SD in the AD patients in another study<sup>(4)</sup>. Moran et al. evaluated 215 patients with AD, showing that SD were associated with other behavioral symptoms, notably aggressiveness ( $p = 0.009$ )<sup>(16)</sup>. Sedentarism and the amount of nighttime sleep were significant predictors of an aggressive behavior during shower baths in nursing home residents with dementia<sup>(19)</sup>. It seems that sleep-disordered breathing is associated with some forms of agitation in AD patients, particularly with aggressive behavior and manual manipulation during daytime and verbal agitation at night<sup>(20)</sup>. Further research is required to establish the relationship between SD in AD and behavioral symptoms.

There has been discussion in the literature regarding the role of education level in SD. For example, in Thailand no formal education was associated with insomnia in older people with a mild to moderate degree of poor cognitive ability<sup>(21)</sup>. On the other hand, using the Sleep Disorders Inventory, worse scores were not associated with education level in persons with AD<sup>(22)</sup>. The mechanism regarding the association of SD and educational level is not clear, but Marchi et al. evaluated 215 Brazilian individuals (not only aged) and found that the uneducated group and persons with little schooling showed more association with insomnia ( $p$  value = 0.001). They argued that individuals with less education usually correspond to those with a lower spending power and more prone to unemployment and consequently more exposed to anguish<sup>(23)</sup>.

We believe that SD in demented patients is under estimated and it is therefore important to highlight this aspect to doctors. Perhaps, the incidence and prevalence of SD could be higher. When it comes

together, behavioral problems stand out and guide treatment, often with antipsychotics. Furthermore, SD are common in behavioral and psychological symptoms of dementia<sup>(24,25)</sup>. In fact, caregivers complain more often that SD occur in patients with behavioral and psychological symptoms of dementia, and questionnaires are not able to differentiate between SD and behavioral and psychological symptoms of dementia. Many times these SD appear only as daytime sleepiness and questionnaires are not able to capture it.

Therefore it is important that SD in dementia be recognized and treated appropriately. The recognition of associated symptoms may help in determining the cause of SD in demented patients<sup>(16)</sup>. Effective treatment of SD in AD is likely to improve the quality of life for both patient and caregiver and to prevent institutionalization. Antidepressants are a suitable option for the treatment of SD in demented patients<sup>(26)</sup>.

The important limitation of a retrospective study is that the database only can include information originally collected in the patient's charts. We do not know about the patients who died, and if any presented SD. Among other limitations are: the accuracy of information obtained from caregivers, the predominance of one gender and the prevalence of patients with low educational level.

The impact of psychoactive medications was not analyzed. Despite the difficulties already discussed, the lack of polysomnographic data to identify SD such as obstructive sleep apnea can be considered a limitation, thus overestimating the results. However, the use of complex diagnostic procedures is not suitable for prevalence studies like this. Information from caregivers is not always accurate. The burden of the caretaker may be lessened if the patient with dementia spends ample time asleep or in a state of relative calm<sup>(4)</sup>. Caretakers may therefore request medication to induce sleep to the patient.

## CONCLUSION

The incidence of SD in this cohort was elevated. In this study, SD during the follow-up period were associated with educational level less than 8 years and aggressiveness. Studies such as ours provide guidelines to develop longitudinal research, and to define more specific parameters of this relationship.

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