Austin Alzheimer's and Parkinson's Disease

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Research Article

Alzheimer's Disease and Sleep Disorders: A Descriptive Study of Actigraphic and Clinical Presentation Based on Neuropsychiatric Inventory

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Received: January 21, 2015; **Accepted:** July 14, 2015; **Published:** July 18, 2015

Abstract

Sleep disorders are very common in Alzheimer's disease. This study describes the clinical and actigraphic aspects of the sleep pattern of 41 Alzheimer's disease patients identified with sleep disorders by means of the neuropsychiatric inventory. The clinical protocol used to assess sleep quality included eight categories of sleep complaints. In addition, each caregiver rated his/her own distress level according to a five-point scale. The most common primary sleep disorders found among elderly participants were: to wake caregivers during the night (n = 39; 95.1%) and to get up during the night (n = 33; 80.4%). Actigraphic measures confirmed the clinical observation with the nighttime total sleep time = 311.2 ± 91.6 minutes, awakenings = 25.9 ± 8.7 per night and nighttime wake after sleep onset = 198.5 ± 78.4 minutes. Subjects compensated the lack of sleep at night by sleeping and napping during the day: daytime total sleep time = 152.6 ± 97.3 minutes and naps = 32.2 ± 15.8 per day. Most caregivers (70.7%) rated their distress level as moderate/extreme. The authors advocate that further studies and trials focused on the profile of patients, the methods described and types of sleep disorders should be carried out.

Keywords: Sleep disorders; Insomnia; Alzheimer's disease; Neuropsychiatric evaluation; Outpatient care

Introduction

Sleep disorders (SD) are very common in Alzheimer's disease (AD) and studies have identified prevalence of up to 40% in many AD stages [1]. In addition, there is evidence that variance in the sleep–wake cycle directly influences the Aβ levels in the brain tissue [2].

Among the many types of sleep disorders, increased occurrence and length of nocturnal awakenings and increased frequency of daytime napping are the most frequent [3].

Two clinical trials have been recently conducted to examine possible changes in the sleep parameters of AD patients with SDs after use of either trazodone or mirtazapine compared to those using placebo [4,5]. The aim of this report is to describe the overal clinical and actigraphic aspects of the sleep pattern of subjects included in these two clinical trials and characterize the main sleep problems in AD patients, thus contributing to further studies.

Methods

Individuals were recruited among outpatients of the Geriatric Medical Centre of the University's General Hospital from February 2010 to March 2014. This hospital is a reference center for the diagnosis and treatment of dementia in the Brazilian Federal District. The study was previously approved by the University of Brasilia Ethics Research Committee. Written informed consent was obtained from all participants.

The inclusion criteria were: age ≥ 60 years; probable AD [6]; caregiver or family member able to provide informed consent and to follow the patient so to provide information on the study variables; presence of sleep disorders causing emotional distress to caregivers (score ≥1 in the neuropsychiatric inventory - NPI) [7]; regular use of medications for at least 4 weeks prior to the screening visit; possibility of placing an actigraph to a mobile upper limb. Exclusion criteria were the following: sleep disorders associated with acute illness, delirium or psychiatric disease; clinically significant movement disorder; severe agitation; unstable medical condition.

Patients were assessed by wrist actigraphy for a period of 7 to 9 days at baseline (to determine the sleep profile) and for 2 weeks during intervention (mirtazapine, trazodone or placebo). The first two trials were aimed at comparing pre- and post-intervention parameters, but only data of the first week (pre-intervention) were used.

The protocol used for the sleep quality clinical assessment included NPI (Nighttime Behavior item), which investigates the following aspects: "Does the patient have difficulty sleeping (not including if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?" Considering the questions above, the following categories were defined to classify the outcomes observed: 1) difficulty falling asleep; 2) getting up during the night; 3) awaking caregivers during the night; 4) wandering, pacing, or getting involved in inappropriate activities at night (nocturnal perambulation); 5) awaking too early in the morning; 6) other nighttime behaviors (sleep talking); 7)sleeping excessively during the day; 8) waking up at night, dressing and planning to go out; 8) caregiver distress. In addition, caregiver had to

Citation: Camargos EF, Scoralick FM, Louzada LL, Quintas JL and Nóbrega OT. Alzheimer's Disease and Sleep Disorders: A Descriptive Study of Actigraphic and Clinical Presentation Based on Neuropsychiatric Inventory. Austin Alzheimers J Parkinsons Dis. 2015;2(1): 1019.

rate his/her own distress level according to a five-point scale from 0 - no distress, 1- minimal, 2 - mild, 3 - moderate, 4 - moderately severe, 5 - very severe or extreme distress [8].

The actigraphic results were based on the nocturnal period (defined as a continuous 12-h time period from 8:00 pm to 8:00 am) and daytime period (12-h diurnal period from 8:00 am to 8:00 pm). The following variables of patients were defined: 1) NTST - Nighttime total sleep time (in minutes); 2) WASO - Nighttime wakening after sleep onset (in minutes) up to final awakening; 3) Awakenings - Nighttime number of awakenings after sleep onset up to final awakening; 4) DTST - Daytime total sleep time (in minutes); 5) Naps - Number of daytime naps; 6) %Sleep - percentage of time asleep during the nocturnal period.

The actigraphs used in this study were Actiwatch® (Respironics, Inc.) and its software (Actiware®, version 5.59.0015, 2010). Actigraphs were used on participants' non-dominant wrist and the following parameters were analyzed: 1) wake threshold selection = medium; 2) wake threshold value = 40; 3) sleep interval detection algorithm = 10 immobile minutes for sleep onset and sleep end. There is evidence of good correlation between actigraphy and polysomnography measures in patients with dementia and it is appropriately used for measuring sleep in intervention studies with Alzheimer's disease patients [9].

Other scales applied for all patients were: Cornell Depression Scale [10]; Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) [11]; Clinical Dementia Rating (CDR) [12]; Katz Index of Independence in Activities of Daily Living [13].

Data processing and statistical analysis were performed using SAS v.9.2 Software (SAS Institute, Inc., 1999) with descriptive analyses expressed as mean values (and standard deviations) or proportions, when appropriate.

Results

Forty-one subjects diagnosed with AD and SD were included in this study. The mean age of subjects was 81.4 ± 7.7 years, with women comprising 68.2% of the sample. The mean MMSE score of 11.0 ± 6.8 and the highly frequent CDR scores of 2 and 3 were compatible with moderate to severe dementia as the most common phenotypes. Demographic and descriptive variables are described in Table 1.

Clinical outcomes

The primary sleep disorders found among elderly participants according to NPI were: to wake caregivers during the night (n = 39; 95.1%); to get up during the night (n = 33; 80.4%); to wander, pace, or get involved in inappropriate activities at night (nocturnal perambulation) (n = 29; 70.7%); difficulty in falling asleep (n = 24; 58.5%); to wake too early in the morning (n = 22; 53.6%); excessive daytime sleep (n = 20; 48.7%); and to wake up at night, dress, and plan to go out (n = 19; 46.3%). Other nighttime behaviors incompatible with good nighttime sleep (e.g.: sleep talking) were found in 22 subjects (53.6%).

Twenty nine (70.7%) of the caregivers considered their distress level as moderate/extreme, and only three (7.3%) rated their distress level as minimal.

Actigraphic outcomes

The actigraphic parameters observed in elderly participants were:

Table 1: Demographic and descriptive variables of Alzheimer patients with sleep disorders (n = 41).

Variables[#]	
Sex	
Female	28 (68.2)
Male	13 (31.8)
Marital status	
Married	18 (43.9)
Widower/Widow	15 (36.5)
Other	8 (19.6)
Educational level	
Illiterate	8 (19.5)
< 4 years	16 (39.0)
≥ 4 years	17 (41.5)
CDR	
1	17 (41.5)
2	13 (31.7)
3	11 (26.8)
Cornell Depression Scale	8.4 ± 4.8
BEHAVE-AD	12.1 ± 8.1
Katz Index	6.4 ± 5.2
Treatments for AD	
Anticholinesterase	21 (51.2)
Memantine	9 (21.9)
Antipsychotics	
Yes	4 (9.7)
Hypnotics	
Yes	2 (4.8)

[#]: Data are expressed as mean ± SD or absolute number and proportion in parenthesis for each group of patients; AD: Alzheimer's disease; CDR: Clinical Dementia Rating

NTST = 311.2 ± 91.6 minutes; WASO = 198.5 ± 78.4; Awakenings = 25.9 ± 8.7 per night; %sleep = 56.4 ± 14 per night; DTST = 152.6 ± 97.3; Naps = 32.2 ± 15.8.

Discussion

The actigraphic and clinical results showed that to get up during the night and to wake caregivers were the most common types of sleep disorders in AD patients. This clinical profile was corroborated by actigraphic measures that demonstrated fragmented nighttime sleep (mean of 26 awakenings/night) and short total sleep time (average of 5 hours/night), with poor sleep efficiency (56%) and increased WASO (3 hours/night)on average. In a population-based study conducted elsewhere with 205 AD patients, it was observed that waking the caregiver up at night was the most distressing aspect [14], with some change in the pattern of sleep disturbance due to the worsening of cognitive, functional and depression statuses. In our study, the Cornell Depression Scale expressed that most patients had depressive symptoms, but the impact of this finding on sleep has not been assessed. In addition, the profile shown above indicates that a common compensation for the lack of sleep consisted on an average of 2.5 hours of daytime sleep.

A longitudinal study evaluating the sleep/wake pattern of patients with AD found that the frequency of waking episodes after sleep onset (WASO) increases over the course of the disease [15]. This event has a huge impact on the quality of life of patients with dementia and their caregivers, increasing the risk of institutionalization [16] and having a negative impact on the health of caregivers, mainly their sleep. Studies have found that caregivers of patients with dementia take psychotropic drugs (benzodiazepines and antidepressants) more frequently than those of patients without dementia [17].

Another fact that attracts attention is about inappropriate activities at night occurring to around 70% of the sample. Inappropriate activities include intention or action of "going home", "organizing closets", "preparing food", "going to parents' home", among others. Despite being frequent and stressful for caregivers and family members, these behaviors can be non-pharmaceutically addressed. Some studies with daily interventions aiming at improving nighttime sleep have been conducted by McCurry et al. (2011), who evaluated the efficacy of walking, light exposure and a combination treatment (walking, light and guided sleep education) to improve the sleep quality of demented patients [18]. Participants in active treatment were asleep for on average 37 min per night more than non-treated subjects. Considering how aspects regarding sleep disorders in AD patients impact caregivers and their families, these sleep disorders should be carefully studied. To date, there are many intervention studies on sleep disorders using non-pharmacological and behavioral/environmental approaches [9].On the other hand, there are few studies using drug intervention [19]. Recent systematic review by the Cochrane Library identified lack of evidence on this topic, with no evidence regarding the beneficial effects of melatonin in sleep disorders in AD patients with moderate to severe dementia, but some evidence to support the use of low dose (50 mg) of trazodone in this scenario of outpatient care of community-dwelling patients [19].

Actigraphic analysis is an adequate method to measure sleep in AD. Although polysomnography is considered the gold standard in sleep studies, its use in this group of patients is unfeasible [9,19]. Gaining a few minutes in TST and reducing WASO can also reduce caregiver burden. According to the authors, actigraphic analyses allow assessing these aspects with greater accuracy in cognitively impaired subjects.

Our study has some limitations. Firstly, the limited sample size that makes the study prone to reveal only the most frequent events. Secondly, the cross-sectional design that does not allow incidence analyses. It is possible that some types of SD disappear or decrease in intensity over time. Thirdly, choosing a 12-hour nighttime period to define the nocturnal period can be questionable. Longer actigraphic measures could show more homogenous analysis. However, the number of days of recording required for a suitable baseline in terms of "sleep pattern" has not been established. For estimates of sleep and 24-h activity rhythm variables, an acceptable estimate required more than 7 days of recording [9,20].

In conclusion, this sample of patients with Alzheimer's disease and sleep disorders shows a clear pattern of poor sleep quality as evaluated by NPI, with a marked shortage in total sleep time and enhanced frequency of nighttime awakenings based on actigraphic measures. Given the frequency of sleep complaints described and the methods by which these traits were diagnosed, further studies and trials focused on the profile of patients as those characterized here should be carried out.

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Austin Alzheimers J Parkinsons Dis - Volume 2 Issue 1 - 2015
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Citation: Camargos EF, Scoralick FM, Louzada LL, Quintas JL and Nóbrega OT. Alzheimer's Disease and Sleep Disorders: A Descriptive Study of Actigraphic and Clinical Presentation Based on Neuropsychiatric Inventory. Austin Alzheimers J Parkinsons Dis. 2015;2(1): 1019.