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Clinical Study

Assessment of sleep satisfaction in patients with dementia due to Alzheimer's disease

Fabricio Ferreira de Oliveira [a,b,*], Paulo Henrique Ferreira Bertolucci [a], Elizabeth Suchi Chen [b], Marilia de Arruda Cardoso Smith [b]

[a] Department of Neurology and Neurosurgery, Escola Paulista de Medicina, Federal University of São Paulo (UNIFESP), Rua Botucatu 740, Vila Clementino, CEP 04023-900 São Paulo, SP, Brazil
[b] Department of Morphology and Genetics, Escola Paulista de Medicina, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil

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ABSTRACT

Sleep length and architecture are potential markers of progressive cognitive impairment, while neuropsychiatric symptoms and APOE4− haplotypes have been associated with more sleep complaints in patients with dementia due to Alzheimer's disease (AD). In this cross-sectional study, we sought to investigate which factors might be related to sleep satisfaction in patients with AD. A total of 217 consecutive patients with AD were assessed for demographic features, neuropsychiatric symptoms, cognitive decline, functional impairment for activities of daily living, caregiver burden, APOE haplotypes, self-reported sleep satisfaction and length of sleep. Statistical comparisons were conducted with significance at $p < 0.05$. Concerning sleep complaints, 179 patients (82.5%) reported satisfactory sleep, while 38 (17.5%) were unsatisfied, with no relation to age, sex, APOE haplotypes, obesity, education, marital status, alcohol consumption or smoking found. Length of sleep ($p = 0.011$) and behavioural symptoms ($p = 0.009$) had significant associations with sleep satisfaction. Length of sleep was positively correlated with apathy ($p = 0.014$) and scores on the Clock Drawing Test ($p = 0.015$), and inversely correlated with anxiety ($p = 0.015$) and independence for instrumental activities of daily living ($p = 0.003$). Patients who were treated with memantine ($p = 0.02$) or anti-psychotics ($p < 0.01$) had longer duration of sleep. In conclusion, behavioural symptoms had strong associations with sleep satisfaction, which is highly correlated with length of sleep in patients with AD. Functional independence, apathy, anxiety, use of memantine or anti-psychotics, and scores on the Clock Drawing Test were significantly associated with length of sleep in this sample.

1. Introduction

Sleep length and architecture deteriorate with normal aging, mild cognitive impairment and dementia, and could represent potential markers of progressive cognitive impairment [1,2]. Nonetheless, insomnia is not a normal aspect of aging [3]. Recurrently observed sleep disturbances in patients with dementia due to Alzheimer's disease (AD) include difficulty to initiate sleep, fragmented sleep with frequent awakenings, decreased total sleep time with early awakening, waking up at night and thinking that it is daytime, night-time wandering, daytime napping, increased latency to first rapid eye movement (REM) sleep episode, decreased slow-wave sleep, impaired sleep efficiency, sleep-disordered breathing (mostly obstructive sleep apnoea) and sundowning [3,4]. Regarding characterisation of the decrease in total sleep time, provisional diagnostic criteria for insomnia in patients with AD were designed in 2003 [5], based on the reduction of 25% of total nocturnal sleep relative to the premorbid nocturnal sleep pattern, or fewer than 6 hours of sleep at night.

Sleep disturbances increase with advancing dementia severity, and may predict a faster cognitive decline, mostly in the mild to moderate stages of AD [6]. Insomnia may also lead to more patient institutionalisation, increase risk of falls and mortality, and impact caregiver burden [3,5,7]. Other non-cognitive complications may result from sleep-disordered breathing, which increases cardiovascular risk and agitation, and is not unusual in patients with AD [5,7,8].

A recent actigraphic study showed that cerebrospinal fluid Aβ42 levels were associated with worse sleep efficiency and more frequent napping (three or more days per week) in the preclinical stages of AD [9]. This is particularly important considering that

* Corresponding author. Tel.: +55 11 5576 4139; fax: +55 11 5575 5240.
E-mail address: fabricioferreiradeoliveira@hotmail.com (F.F. de Oliveira).

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Aβ increases during wakefulness and decreases during sleep, but it does not seem possible at the moment to objectively address whether poor sleep causes AD or, *vice versa*, if dementia is the cause of sleep disruption.

The suprachiasmatic nucleus of the hypothalamus is the primary circadian pacemaker in the mammalian brain, and is indirectly connected to the ventrolateral preoptic area [10]; both of these hypothalamic structures are susceptible to age-related volumetric reductions, possibly contributing to increased sleep fragmentation and slow-wave sleep deficits found in the elderly [10,11]. The hypothalamic hypocretin system has been shown to be affected in severe AD, with decreased neuronal numbers and lower cerebrospinal fluid hypocretin-1 levels, which may be related to the amount of daytime napping [12]. Slow-wave sleep has been consistently implicated in declarative memory consolidation, a process that seems to involve connections between the hippocampus and neocortical areas [2]. Moreover, cholinergic dysfunction originating in the nucleus basalis of Meynert and mesopontine neurons of the pedunculopontine tegmentum and the laterodorsal tegmentum has been associated with REM sleep deficits in patients with AD [3,10].

Correlations between sleep satisfaction and neuropsychiatric symptoms during cognitive decline in AD are still imprecise. An earlier preliminary study from our group [13] confirmed that behavioural symptoms and low education levels are associated with more sleep complaints in patients with AD, and also that sleep satisfaction and length of sleep are closely related. In this study, with a more comprehensive evaluation of a larger sample, we sought to investigate which factors might be related to sleep satisfaction in patients with AD.

2. Subjects and methods

This is a cross-sectional study in which consecutive outpatients with AD [14] in different stages were recruited from the Behavioural Neurology Section of Hospital São Paulo, Brazil from November 2010 to February 2013 (28 months). After diagnostic confirmation, they were assessed for age, sex, education level, marital status, estimated age of onset of the dementia syndrome, quantification of current alcohol consumption and/or smoking, use of cholinesterase inhibitors or anti-depressants, use of antipsychotics or anti-epileptic drugs, number of different medications taken daily, body mass index, and scores on the Neuropsychiatric Inventory [15], Mini-Mental State Examination [16], Severe Mini-Mental State Examination [17], Clinical Dementia Rating (CDR) [18], a 15-item Clock Drawing Test (free drawing) [19], the Index of Independence in Activities of Daily Living [20], Lawton's Scale for Instrumental Activities of Daily Living [21], and the Brazilian version of the Zarit Caregiver Burden Interview [22]. Patients were asked if their sleep was satisfactory (yes or no), what factors might interfere with it, and the mean amount of time slept each day, with confirmation by their caregivers. The length of sleep had to be as precise as possible, including daytime naps, and excluding eventual time spent in bed without sleeping. In case patients were unable to describe their sleep, preference was given to caregiver reports. All cognitive evaluations and body mass index measurements were conducted on weekdays in the morning by the same examiner (F.F.O.).

Diagnosis of AD was in accordance with National Institute on Aging – Alzheimer's Association criteria [14]. Obesity was diagnosed when the body mass index was over 30 kg/m^2.

For the validated version of the Clock Drawing Test [19] that was used in this study, patients were instructed to freely draw a clock that said 11:10, setting the hands and numbers on the face (repetition was allowed). Scoring comprised the following 15 items, each scored as 0 or 1: outer circle present and closed; acceptable circle diameter; intact sequence 1–12, with no omissions or intrusions; only Arabic numerals; correct sequential order of the numerals; paper not rotated for number placement; proper symmetrical spacing; all numbers inside the circle; only two hands present; any mark to indicate the hour; any mark to indicate the minute; minute hand longer than hour hand; no pointless intrusions; both hands connected, or up to 2 mm space between them; and the centre of the clock drawn or inferred where hands meet.

The Index of Independence in Activities of Daily Living [20] reflects behavioural levels of six sociobiological functions: bathing, dressing, toileting, transfer, continence, and feeding. Each function was scored as 0 for dependency or 1 for independence, according to information from caregivers, with an index total of 0 to 6. A trichotomous version (1 = unable; 2 = able with help; 3 = able without help) of Lawton's Scale for Instrumental Activities of Daily Living [21] was employed, with scores for using the telephone, getting to places beyond walking distance, grocery shopping, meal preparation, housekeeping, doing handyman work, doing laundry, taking own medications, and handling finances. This information had to be obtained from caregivers, with a possible total score between 9 and 27.

After blood samples were collected from all patients in tubes with EDTA 0.1%, genomic DNA was extracted for genotyping. APOE haplotypes were determined for all patients (single nucleotide polymorphisms rs7412 and rs429358 assessed by way of real-time polymerase chain reactions using TaqMan SNP Genotyping Assays (Life Technologies, Carlsbad, CA, USA). Real-time polymerase chain reactions (PCR) were undertaken on the Applied Biosystems 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) following the standard protocols of the manufacturer.

Statistical comparisons among groups according to APOE haplotypes or sleep satisfaction were conducted by way of Mann–Whitney *U* test (two groups) or Kruskal–Wallis test (more than two groups). A multiple regression model was employed for correlations among the continuous variables that might impact the daily quantity of sleep (dependent variable) with 13 degrees of freedom, and also independently for correlations among each item from the Neuropsychiatric Inventory and the daily quantity of sleep with 10 degrees of freedom. Fisher's exact test was employed for comparisons between categorical variables. The threshold of significance was set at $p < 0.05$.

This study is part of the research project 1067/10 (CAAE 0540.0.174.000-10) approved by the Ethics Committee of Hospital São Paulo, Federal University of São Paulo (UNIFESP), on August 2010. All invited patients and their respective caregivers agreed to participate on the research and signed the informed consent form before the evaluation, with no exceptions.

3. Results

A total of 217 patients were included, with 147 females (67.7%) and 70 males (32.3%); 109 (50.23%) were married, while six (2.76%) were divorced, 19 (8.76%) were single, and 83 (38.25%) were widowers; 56 (25.8%) had a history of alcohol consumption, and 11 (5.1%) were regularly drinking at the time of the survey; 79 (36.4%) had a smoking history, and 14 (6.5%) were regular smokers at the time of the survey. Obesity was diagnosed in 36 patients (16.6%). Detailed demographic and test results, along with statistical differences according to sleep satisfaction, are found in Table 1.

Table 2 shows results according to APOE haplotypes, with 114 APOE4+ and 103 APOE4− cases. Earlier onset of dementia was correlated with APOE4+ in patients with CDR of 2.0 (n = 104, $p = 0.019$) and with the E4/E4 haplotype in patients with CDR of 1.0 (n = 83, $p = 0.007$). APOE haplotypes had no significant