Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-122014
IOS Press

Sleep in Frontotemporal Dementia is Equally or Possibly More Disrupted, and at an Earlier Stage, When Compared to Sleep in Alzheimer's Disease

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Handling Associate Editor: Elio Scarpini

Accepted 18 June 2013

Abstract.

Background: Conversely to other neurodegenerative diseases (i.e., Alzheimer's disease, AD), sleep in frontotemporal dementia (FTD) has not been studied adequately. Although some evidence exists that sleep-wake disturbances occur in FTD, very little is known regarding sleep macrostructure and/or primary sleep disorders.

Objective: To investigate these issues in this population and compare them to similar issues in AD and in healthy elderly (HE).

Methods: Twelve drug-naïve behavioral-variant FTD (bvFTD) patients (7 men/5 women) of mean age 62.5 ± 8.6 years were compared to seventeen drug-naïve AD patients (9 men/8 women) of mean age 69.0 ± 9.9 years and twenty drug-naïve HE (12 men/8 women) of mean age 70.2 ± 12.5 years. All participants were fully assessed clinically, through a sleep questionnaire, an interview, and video-polysomnography recordings.

Results: The two patient groups were comparably cognitively impaired. However, compared to FTD patients, the AD patients had a statistically significant longer disease duration. Overall, the sleep profile was better preserved in HE. Sleep complaints did not differ considerably between the two patient groups. Sleep parameters and sleep macrostructure were better preserved in AD compared to FTD patients, regardless of primary sleep disorders, which occurred equally in the two groups.

Conclusions: With respect to AD, FTD patients had several sleep parameters similarly or even more affected by neurodegeneration, but in a much shorter time span. The findings probably indicate a centrally originating sleep deregulation. Since in FTD patients sleep disturbances may be obvious from an early stage of their disease, and possibly earlier than in AD patients, physicians and caregivers should be alert for the early detection and treatment of these symptoms.

Keywords: Alzheimer's disease, dementia, frontotemporal dementia, sleep

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INTRODUCTION

Frontotemporal dementia (FTD) has increasingly become recognized as a major cause of dementia responsible for 12% of early-onset dementia cases (<65 years) [1], and it is nearly as common as Alzheimer's disease (AD) in early-onset dementia patients of memory clinics [2]. Behavioral symptoms, progressive language deficits, and personality changes predominate in FTD. The differential diagnosis between FTD and AD is often problematic [3, 4], given the fact that frontal executive deficits and behavioral disorders, which are cardinal clinical features of FTD, are frequently found in early-onset AD as well.

Sleep disorders are considered to be important among the non-cognitive symptoms often encountered in dementia. In particular, sleep disturbances such as nighttime sleep fragmentation, increased sleep latency, and increased daytime napping have been described as a significant problem in the course of the dementing illness that may seriously impact the patients' and caregivers' quality of life [5]. Cross-sectional clinical and epidemiological studies have reported that up to 40% of patients with AD have sleep disturbances [6]. Polysomnographic (PSG) studies of AD patients have shown a high prevalence of obstructive sleep apnea (OSA) and altered sleep architecture with frequent awakenings, reduced REM sleep percentage, and increased REM sleep latency [7, 8], especially during the advanced stages of the disease. Sleep in FTD has not been examined adequately. There are only a few studies assessing sleep with inventories, sleep diaries, and actigraphy [9, 10], and a couple of PSG studies that evaluated sleep in FTD patients [11, 12]. All existing studies have shown that sleep in FTD is significantly affected.

In order to provide further details on sleep in FTD, the present study polysomnographically assessed sleep in drug-naïve FTD patients, also controlling for primary sleep disorders. Furthermore, sleep parameters, which may have a pathophysiological and prognostic significance, were compared with a matched group of drug-naïve AD patients and another matched group of healthy elderly controls (HE).

MATERIALS AND METHODS

Subjects

Twelve behavioral-variant FTD (bvFTD) patients (7 men/5 women) of mean age 62.5 ± 8.6 years, 17 AD patients (9 men/8 women) of mean age 69.0 ± 9.9 years, and 20 HE (12 men/8 women) of mean age 70.2 ± 12.5 years, all drug-naïve (for drugs that affect the central nervous system, CNS), participated in the study. The patients were referred to the Cognitive Neurology-Extrapyramidal Disorders Unit of the Department of Neurology at the University of Athens Medical School during a three-year period (2007–2010) for dementia diagnosis. The referral guidelines, the clinical and laboratory workup of patients, and the criteria applied for diagnosis have been described in detail elsewhere [2]. General mental state and severity of dementia were assessed with the Mini-Mental State Examination (MMSE) [13] and the Clinical Dementia Rating scale (CDR) [14]; neuropsychiatric symptoms/behavioral disturbances were evaluated with the Neuropsychiatric Inventory (NPI) [15] and the Frontal Behavioral Inventory (FBI) [16]. The HE group included drug-naïve (for drugs that affect the CNS) subjects who were free of cognitive complaints/disease (MMSE >28), with no history or complaints of sleep disorders or under any related therapy (confirmed through a sleep disorders interview); subjects who did not satisfy all the above-mentioned criteria were not enrolled in the study.

Patients and controls suffering from major organic disorders (e.g., tumors, rheumatic diseases, chronic obstructive pulmonary disease and related respiratory diseases), or from serious painful or other diseases that could influence normal sleep, were not enrolled in the study. Moreover, patients and controls did not have any psychiatric history. "Minor" co-morbidities (e.g., high blood pressure) were allowed in the participants (patients and controls) only if they were under treatment for at least 6 months. Written informed consent was obtained from the participants after detailed information on the study objectives and the research protocol was provided to them. The study was carried out in accordance with the Declaration of Helsinki and after scientific and ethics committee approval was obtained.

Sleep evaluation

According to our standard evaluation, all patients (or a relative in cases of patient inability) completed a "yes/no" self-report sleep questionnaire composed of 17 questions concerning sleep schedule, insomnia and relative hypnotic medication, symptoms compatible with the restless leg syndrome, snoring (including severity) and sleep apnea, NREM/REM sleep parasomnias, and excessive daytime sleepiness (EDS). Based on the sleep questionnaire, patients were

thoroughly interviewed by a neurologist trained in sleep medicine. Further information regarding EDS was provided from a standardized questionnaire, the Epworth Sleepiness Scale (ESS) [17].

A diagnostic video-polysomnographic (VPSG) examination (between 11:00 pm and 06:00 am) took place after a first adaptation night in the sleep laboratory. VPSG included six-channel electroencephalogram (using two frontal, two central, and two occipital scalp electrodes referred to the contralateral mastoid (M1 or M2) electrode), two-channel electrooculogram, electromyogram of the submentalis and anterior tibialis muscles bilaterally, blood oxygen saturation recording using a finger pulse oxymeter, respiratory effort sensors placed over the rib cage and abdomen, a snoring vibration sensor, a body position sensor, a nasal cannula pressure transducer, and a thermistor. Sleep stages (scored in 30-s epochs), respiratory events, arousals, and REM sleep without atonia were visually scored according to the criteria described in the AASM manual for the scoring of sleep and associated events [18]. For the diagnosis of a sleep disorder, the clinical and polysomnographic criteria of ICSD-2 were used [19].

Statistical analysis

Statistical analysis was performed using the SPSS v.16 statistical package (IBM Corp., Somers, NY, USA). One-way analysis of variance (ANOVA) with Bonferroni-corrected *post-hoc* tests was used to identify significant differences in VPSG parameters between the three study groups. Independent-sample *t*-tests were used to compare neurocognitive measures (MMSE, CDR, NPI, FBI) and disease duration between FTD and AD patients; Mann-Whitney and Kruskal Wallis non-parametric tests were used for comparisons of dichotomous variables pertaining to subjective sleep measures and sleep history data. For all reported values, the mean and standard deviation ($\pm$SD) were calculated. All statistical inferences were based on 2-tail probability distributions and statistical significance was set at $p < 0.05$.

RESULTS

Neurocognitive measures, subjective parameters, and sleep history of the patients (Table 1)

The patients in the two groups were of comparable cognitive status (mild-to-moderate cognitive decline) and of similar severity regarding neuropsychiatric disturbances (CDR, MMSE, NPI). Behavioral disorders due to frontal degeneration (FBI) were significantly more prominent in the FTD patients, as expected. There was a statistically significant longer disease duration in the AD group compared to the FTD one (Table 1).

Table 1
Neurocognitive measures and subjective parameters of the patients

Parameter	AD ($n = 17$)	FTD ($n = 12$)	p
Clinical Dementia Rating Scale	1.0 ± 0.54	1.3 ± 0.63	n.s.[1]
Mini-Mental State Examination	17.9 ± 5.63	20.8 ± 3.87	n.s.[1]
Neuropsychiatric Inventory	11.8 ± 8.71	16.3 ± 8.86	n.s.[1]
Frontal Behavioral Inventory	10.9 ± 6.60	23.0 ± 9.10	**0.001**[1]
Disease duration (years)	2.8 ± 1.71	1.5 ± 0.72	**0.013**[1]
Epworth Sleepiness Scale >10	1 (6%)	4 (33%)	n.s.[2]
Sleep Disordered Breathing	4 (24%)	3 (25%)	n.s.[2]
Insomnia	1 (6%)	2 (17%)	n.s.[2]
Restless Leg Syndrome	1 (6%)	1 (8%)	n.s.[2]
REM Sleep Behavior Disorder symptoms	0 (0%)	1 (8%)	n.s.[2]
NREM sleep parasomnia (sleeptalking)	4 (24%)	1 (8%)	n.s.[2]

[1]Independent-sample *t*-test; [2]Mann-Whitney test.

Regarding subjective parameters, as assessed by the sleep questionnaire and the interview, these were as follows: EDS, as assessed by the ESS score, was more often above normal (cut-off >10) in FTD compared to AD patients. Primary sleep disorders, i.e., symptoms of sleep disordered breathing (SDB) such as heavy snoring and witnessed apneas, or sleep-initiation insomnia (difficulty falling asleep), did not differ between the two groups. One FTD patient had a history compatible with REM sleep behavior disorder, whereas NREM sleep parasomnias (sleeptalking) were more frequently reported by AD patients. None of the above differences reached a statistical significance (Table 1).

Video-polysomnography (VPSG)

Table 2 shows the results of VPSG and Table 3 shows the prevalence of indices of disturbed sleep in the three groups.

Despite the fact that there were no statistically significant differences, except in the number of NREM/REM sleep cycles, and a trend for significance in LREM ($p = 0.06$), in general, the results of VPSG in the two patient populations showed that the AD patients had a better preserved sleep than the FTD patients. When the sleep parameters of AD and FTD patients were compared with those of HE subjects, some indices which characterize and promote good sleep seemed to be significantly worse in the patient populations. Hence, compared with HE, both AD and

Table 2
Video-polysomnographic (VPSG) parameters in the three groups

VPSG parameters	AD ($n=17$) (Mean ± SD)	FTD ($n=12$) (Mean ± SD)	HE ($n=20$) (Mean ± SD)	AD/FTD (p)*	AD/HE (p)*	FTD/HE (p)*
Sleep onset (min)	19.1 ± 22.94	36.0 ± 26.14	23.1 ± 27.78	n.s.	n.s.	n.s.
Total sleep time (min)	318.4 ± 74.09	283.0 ± 80.26	355.8 ± 65.15	n.s.	n.s.	**0.025**
Sleep efficiency (%)	77.8 ± 15.65	72.1 ± 17.98	80.3 ± 10.46	n.s.	n.s.	n.s.
LS1 (min)	19.1 ± 22.94	36.0 ± 26.13	24.9 ± 27.28	n.s.	n.s.	n.s.
LS2 (min)	33.9 ± 33.16	60.5 ± 35.61	49.5 ± 34.86	n.s.	n.s.	n.s.
LS3 (min)	74.1 ± 46.19	102.2 ± 58.97	84.6 ± 24.53	n.s.	n.s.	n.s.
LREM (min)	114.2 ± 61.78	188.9 ± 98.83	119.1 ± 78.11	n.s.	n.s.	n.s.
N1 %	17.7 ± 8.43	16.3 ± 8.27	8.8 ± 5.93	n.s.	**0.002**	**0.024**
N2 %	31.7 ± 14.00	35.9 ± 13.30	53.8 ± 10.01	n.s.	**<0.000**	**0.001**
N3 %	18.7 ± 13.55	17.6 ± 9.36	19.4 ± 10.42	n.s.	n.s.	n.s.
REM %	12.7 ± 7.20	11.1 ± 6.17	17.9 ± 7.14	n.s.	n.s.	**0.045**
Wake %	18.9 ± 14.12	20.8 ± 15.25	15.1 ± 10.07	n.s.	n.s.	n.s.
Arousal index (no/h)	19.3 ± 12.38	26.4 ± 17.60	21.2 ± 8.52	n.s.	n.s.	n.s.
NREM/REM cycles	3.5 ± 1.27	1.9 ± 1.11	3.8 ± 1.25	**0.007**	n.s.	**<0.000**
Apnea hypopnea index	19.0 ± 18.68	23.2 ± 18.54	3.7 ± 1.45	n.s.	**0.035**	**0.010**
Periodic leg movement index	16.4 ± 35.51	13.6 ± 26.08	22.5 ± 12.76	n.s.	n.s.	n.s.

L (S1, S2, S3, REM), Latency. *One-way analysis of variance (ANOVA) with Bonferroni-corrected *post-hoc* tests.

Table 3
Prevalence of indices of disturbed sleep in the three groups

Indices of disturbed sleep	AD ($n=17$)	FTD ($n=12$)	HE ($n=20$)
Delayed sleep onset (>30 min)	2 (12%)$^{+}$	7 (58%)	5 (25%)
Reduced sleep efficiency (<80%)	6 (35%)	8 (67%)	9 (45%)
Apnea hypopnea index > 15	7 (41%)*	9 (75%)	15 (75%)
15 < Apnea hypopnea index < 30	4 (24%)	3 (25%)	0 (0%)
Apnea hypopnea index > 30	4 (24%)	4 (33%)	0 (0%)
Respiratory distress index > 15	8 (47%)	6 (50%)	0 (0%)

$^{+}$Kruskal Wallis Test: $\chi^2 = 7.109$, df = 2, $p = 0.029$; *Kruskal Wallis Test: $\chi^2 = 6.141$, df = 2, $p = 0.046$.

FTD groups had significantly more N1% and less N2% and REM% (only for FTD), significantly more Apnea Hypopnea Index (AHI), while FTD patients had significantly less total sleep time (TST) and less NREM/REM cycles than HE subjects. However, there was no significant difference in sleep efficiency (SE) among the three groups. Considering the indices of disturbed sleep (Table 3), sleep onset (SO) was delayed (>30 min) in more than half of FTD patients, in contrast to very few AD patients and few HE subjects. Regarding SE, this was low (<80%) in the majority of FTD patients and in some AD patients; SE was also low in almost half of the HE subjects. More FTD patients and HE subjects than AD patients had an arousal index above 15.

Patients in the three groups had an almost identical body mass index (ANOVA between groups, $p = 0.898$). Respiratory parameters did not differ between the two patient groups, but there was a significant difference between each of these groups and HE (AD versus HE: $p = 0.035$, and FTD versus HE: $p = 0.010$) (ANOVA between groups, $p = 0.007$). The percentages of FTD and AD patients with AHI between 15–30 (sleep apnea of moderate severity) and AHI > 30 (severe apnea) were comparable. In terms of respiratory disturbance (Respiratory Distress Index, RDI), similar percentages of FTD and AD patients had RDI > 15. The Periodic Leg Movement (PLM) index did not differ among the three groups (ANOVA between groups $p = 0.832$). No REM sleep behavior disorder or other parasomnia was recorded.

DISCUSSION

Our findings indicate that sleep in both FTD and AD patients is altered when compared with healthy elderly, mainly concerning sleep structure and presence of SDB. Furthermore, FTD patients, when compared to AD patients, had several sleep parameters similarly or more affected by neurodegeneration in a shorter time span. However, because the sample studied was relatively small, despite the fact that the patient populations were drug-naïve and well-matched for important parameters, no firm conclusions can be drawn. Nevertheless, the present results are in line with recent sleep findings obtained from a large Italian multicenter study of referral centers for dementia that concluded that FTD patients were twice as much affected by sleep disturbances than AD patients [20].

Sleep in FTD has not been examined adequately. The few existing studies which assessed sleep with inventories, sleep diaries, and actigraphy have shown that

FTD patients exhibit a different rest/activity pattern compared with AD patients and controls, suggesting a possible phase delay [9], whereas sleep diary data confirmed a decreased sleep efficiency and a decreased total sleep time in FTD patients. Moreover, Harper et al. [10], who compared the activity and core-body temperature rhythms between AD and FTD patients with advanced disease and healthy elderly controls, found significant differences among the three groups.

Only a couple of studies have polysomnographically evaluated sleep in FTD patients. Pawlak et al. [11] studied the sleep of 12 patients with Pick's disease and compared it with that of an age-matched control group. They concluded that FTD patients had a reduced TST, an increased number of awakenings, and a high percentage of stage 1 sleep with a concomitant reduction of the percentage of the other sleep stages and an absence of stage 4 sleep in advanced cases. Also, REM sleep was often fragmented and with a remarkably short latency, as is observed in severely depressed patients. In accordance, we found that FTD patients compared with a control group of comparable age presented more N1%, less REM%, and less TST. Recently, Kundermann et al. [12] evaluated 6 drug-free FTD patients using PSG and compared sleep parameters with those of 15 drug-free AD patients. Although no significant PSG differences were observed between the two groups, a trend toward an increased REM latency, reduced REM sleep, as well as a decrease in stage 2 sleep was found in AD patients compared to FTD patients; patients with primary sleep disorders, i.e., obstructive sleep apnea and PLM, had been excluded from that study. Despite different methodologies, all three PSG studies, ours included, conclude that sleep in FTD patients may be significantly affected. The present study stands out as the only one that compared sleep in FTD patients with both demented patients and control subjects. Moreover, it is the first study to report data on primary sleep disorders, e.g., sleep apnea and PLM, in FTD.

EDS has been studied in AD but not in FTD. In AD patients, EDS is more prevalent when compared to healthy elderly individuals. This finding has been correlated with the degree of cognitive deficit, but increased daytime sleepiness is present even in patients with mild/moderate AD [21]. EDS in AD has been linked not only to sleep disorders, such as OSA [5, 22], but also to the circadian rhythm deregulation and to the exacerbation of age-related sleep fragmentation [5]. Previous studies have demonstrated that patients with FTD have disturbed sleep with decreased sleep efficiency, increased number of awakenings, decreased total sleep time, and signs of circadian deregulation shown as increased nocturnal and decreased morning activity [9–11]. EDS was the main complaint of the FTD patients in the present study. Obstructive sleep apnea, which occurred in half of our FTD patients, may be connected to sleep fragmentation and EDS. However, disturbed sleep can be due to the observed sleep macrostructure disturbances (e.g., decreased TST, low SE, increased light sleep (N1), increased sleep latencies, and reduced NREM/REM cycles), independent of OSA. In this study, a generally disturbed sleep profile in FTD, comparable or even worse to that in AD and occurring in half the time of disease duration when compared to AD, was shown regardless of the primary sleep disorders that may disrupt sleep initiation and continuity. Thus, in FTD, as in AD, a central origin of sleep deregulation seems probable, and possibly related to the neurodegenerative process itself.

The frontal cortex is believed to be one of the key structures of NREM sleep regulation; moreover, the importance of slow-wave sleep in the restoration of prefrontal cortex function is underlined by various studies on sleep disorders [23]. A recent paper clearly demonstrates that in healthy elderly structural brain changes in the prefrontal cortex contribute to sleep disruption [24], which in turn is related to age-related cognitive decline. Moreover, sleep impairment has been associated with reduced hippocampal-frontal lobe connectivity. It may be implied that such structural/functional changes could be even more pronounced in FTD. In addition to frontal atrophy considerations, the hypothalamus, previously believed to be spared in FTD and known to be damaged in AD and implicated in NREM sleep initiation, may be involved in FTD. A recent neuropathological study reported a significant hypothalamic atrophy in the behavioral variant of FTD, already pronounced within two years of diagnosis [25]. Neurodegeneration in FTD concerns other areas implicated in sleep regulation, such as diencephalic (e.g., thalamic nuclei, basal forebrain) as well as pontine and medullary areas (e.g., locus coeruleus, raphe nuclei, and reticular formation) [10, 26, 27].

OSA was detected in approximately half of the FTD and AD patients of the present study. To our knowledge, there is no other study demonstrating SDB in FTD patients. OSA prevalence increases with age. In a general population study, 32% and 19% of the participants had AHI between 5–14 and >15, respectively [28]. However, OSA is even more prevalent among the demented elderly [8]. Severe OSA may affect memory and executive function and this is a well-documented

cause of reduced cognitive performance [29]. Thus, the diagnosis and treatment of OSA in patients with cognitive dysfunction is important, as shown by the sustained CPAP use in AD patients with OSA, which resulted in a moderate-to-large effect in cognitive measures, depressive symptoms, and daytime sleepiness [30].

In conclusion, corroborating the existing literature, the present study found that both FTD and AD patients had a more disturbed sleep profile when compared to HE of comparable age, even though, as previously reported [31, 32], the HE group in our study showed to a certain extent to have disturbed sleep as well (e.g., increased sleep stage latencies, increased arousal and PLM index). Moreover, we found that FTD patients had a similar or worse sleep disturbance profile with respect to AD patients of comparable age and cognitive status, which seems to develop over a shorter time span. These findings suggest that FTD patients, since the early stage of their disease and apparently earlier than AD patients, already suffer from an altered sleep and may present with remarkable sleep disturbances. This possibility, together with the proven benefit of SDB treatment on cognition, should motivate physicians and caregivers to pay particular attention to the detection and treatment of sleep disorders in FTD patients from the very early stages of the disease.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1840).

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