

Assessment of Sleep Pattern in Egyptian Elderly with Vascular Dementia

A. Alloush¹, H. Sweed¹, A. Abdelnaser², R. El Akkad¹, M. A. Tork², M. Mortada¹, M. Hamdy^{2*}

¹Department of Geriatrics and Gerontology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

²Department of Neurology and Psychiatry, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Email: *mohamedhamdy_neuro2007@yahoo.com

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Abstract

Study Objectives: Growing evidence suggests that sleep disturbances is common in vascular dementia (VaD). The goal of the current study is to assess the disturbance in sleep pattern in patients with VaD, and compare it to healthy normally cognitive elderly individuals. We next studied whether there are meaningful differences in the Subjective sleep assessment: Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI) and sleep measurements by polysomnography (PSG) in VaD patients. **Study design:** Case control study. **Subject and methods:** Overnight PSG recordings and self-reported sleep measures were obtained from 20 healthy elderly subjects and 20 VaD patients at the sleep laboratory. **Results:** This study showed abnormal subjective sleep quality in all patients and revealed that the most common sleep complaints among VaD patients were: excessive daytime sleepiness (EDS), sleep disordered breathing (SDB), insomnia, restless leg syndrome (RLS), periodic limb movements (PLMS) and REM behavioral disorder (RBD) respectively. Moreover, patients spent more time in stage I sleep, but less time in slow wave sleep (SWS) and REM sleep compared to control populations, with delayed REML and less 1st REML. Also, increased sleep fragmentation; wakefulness after sleep onset (WASO) & sleep fragmentation index (SFI), increased arousal index (AI) & PLMS index were detected in VaD patients. Finally, VaD patients had significant high Apnea, Hypopnea and Respiratory Distress Index (RDI) score with high average SpO₂ Desaturation. **Conclusions:** Sleep is significantly impaired in patients with VaD at both the objective and subjective level, which may be used as a diagnostic marker of VaD. SDB is a common feature of VaD and leads to fragmented sleep, increased nocturnal confusion, and excessive daytime sleepiness. Subjective sleep assessment questionnaire (ESS and PSQI) can be used in VaD patients when objective sleep assessment by PSG recordings is difficult to be done. The PSG study of sleep continuity, sleep architecture, and REM sleep may help in the

prevention of progression of VaD.

Keywords

REM and NREM Sleep Disturbances, Vascular Dementia, Alzheimer Dementia, Vascular Cognitive Impairment, Subjective Sleep Assessment, Polysomnography, Brain Magnetic Resonance Imaging

1. Introduction

Vascular dementia (VaD), the second most common cause of dementia after Alzheimer dementia (AD), represents not less than 20% of cases and is expected to increase in coming years [1]. The pervasiveness of both VaD and AD rises dynamically with age, with the risk of VaD doubling every 5.3 years [2]. Vascular-type pathology and mixed pathology are respectively two and three times more likely in demented patients [3]. In Egypt, the dementia prevalence ranged from 2.01% to 5.07% and dementia increased with age, with the rapid increase among those aging >80 [4].

Because of their dependency and negative financial impact upon their families and healthcare providers, VaD is a major public health issue and its prevention playing the crucial role [5].

Sleep is important to normal cognitive functioning, particularly for the formation and consolidation of new memories. Circadian rhythm and sleep complaints are common in the aging population, particularly in those with dementia [6]. In vascular dementia, neuropsychiatric manifestations are very common (90%), and the most common presenting symptoms are sleep disturbances (61%), depression (46%), and apathy (44%). Sleep disturbance is one of the most important domains of behavioral and psychological symptoms in patients with dementia. Past research has demonstrated that sleep disturbance is related to reduce executive function and an increased mortality rate in older adults [7].

Accurately diagnosing sleep disorders in dementia patients can be quite tricky, due to an abundance of underlying causes, mitigating factors and common causal symptoms. Given the rising prevalence of vascular dementia with aging, the development of more sensitive diagnostic and prognostic tools will be critical for elucidating and modifying VaD pathophysiology to alleviate the personal and socioeconomic impact of cognitive decline in the elderly [8]. Also any delay of early detection or corrective treatment of vascular cognitive impairment (VCI) causes the condition to progress to dementia [9]. Also, patients with mixed pathologies have nearly twice the incremental risk of dementia compared with patients with only Alzheimer-type lesions. Consequently, many cases of dementia could be prevented or delayed by targeting the vascular component [10].

In the current study, we assessed the disturbance in sleep pattern by both the subjective sleep assessment; Epworth Sleepiness Scale (ESS) & Pittsburgh Sleep Quality Index (PSQI) and objective sleep measurements by polysomnography (PSG) in pa-

tients with VaD, and compared it to healthy cognitive elderly individuals.

2. Subject and Methods

2.1. Study Subject

Twenty patients with VaD patients according to the criteria of Vascular Dementia in DSM-V [11] (10/10 M/F, mean age: 66.05 ± 2.04) and 20 healthy subjects (10/10 M/F, mean age: 65.25 ± 2.22 y) age and sex matched, were enrolled in the study from the outpatient clinics of Geriatrics, Neurology and Psychiatry in Ain Shams University Hospitals, from December 2017 till December 2018, after the patients or their caregivers signed an informed consent. Sample size calculation was based on a one-way ANOVA study, the total sample of 40 subjects achieves 80% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. Experimental procedures were previously approved by the Ethical Committee for Human Research at the faculty of medicine Ain Shams University.

Both healthy subjects and VaD patients underwent a full medical, neurological, psychiatric history and clinical examinations. Brain magnetic resonance imaging (MRI) was also performed on all candidates. Exclusion criteria were; other types of dementias, psychiatric disorders affecting sleep, and/or major medical illness affecting sleep, the use of medication affecting the sleep-wake cycle. Patients were at mild to moderate stages of VaD, as assessed using the Clinical Dementia Rating (CDR) [12] and the Mini-Mental State Examination. Cognitive assessment included: Mini Mental State Examination (MMSE) was used to provide a simple global measure of cognitive functioning [13]. Mood assessment by Cornell Scale for Depression in Dementia [14] and Taylor Anxiety Scale were used to exclude patients with depression or anxiety [15]. Subjective sleep assessment was assessed using psychometric sleep assessment questionnaire (applied to the caregivers); an Arabic version for sleep evaluation [16]. This instrument includes validated Arabic translations of other sleep assessment scales; 1) The PSQI [17] and 2) Subjective daytime sleepiness assessment using the ESS [18]. Objective sleep assessment was done using PSG. PSG record includes the following parameters; the electroencephalogram (EEG, leads C3-A2 and O1-A2), electrooculogram (EOG), electromyogram of the chin (chin EMG), electrocardiogram (ECG), the abdominal & thoracic respiratory movements, oral & nasal airflows, and arterial oxygen saturation is also measured. The PSG recordings were taken from 22:00 to 7:00 of the following day. The PSG parameters were scored by visual assessment using the standard criteria [19]. The following data were analyzed: a) Sleep efficiency and continuity indices; sleep latency (SL, the time span between “lights out” and onset of the first stage of sleep), sleep efficiency (SE, the percentages of the sleep time for the recording time) and arousal index (AI, a tendency for more wake after sleep onset arousal). b) Hypnogram indices: the percentage of stage I, II, III, IV, Slow wave sleep (SWS) for total sleep time and the percentage of REM sleep for total sleep time (REM %). c)

REM sleep indices, the following were analyzed: REM; duration of REM time in total sleep time, 1st REMD; first REM period duration and REML; REM latency (the time span between sleep onset and onset of the first REM sleep). d) Sleep fragmentation parameters: total sleep time (TST); the time from sleep onset to the end of the final sleep epoch minus time awake, time spent in wakefulness after sleep onset (WASO); the time spent awake between sleep onset and end of sleep and the Sleep fragmentation index (SFI); any sleep stage shift and the total number of awakenings, divided by TST/h. e) Respiratory events includes APNEA, HYPONE, RDI (Respiratory Distress Index) & Oxygen Saturation (SPO2). f) PLMS; periodic limb movements.

2.2. Statistical Analysis

Data were processed by standard analytical procedures [20] to determine the awake time after sleep onset, sleep efficiency, percentage of non-REM sleep in Stages 1 to 3 of sleep, percentage of REM sleep, and REM sleep latency. Results are expressed as mean, standard deviation (SD) or number (%). Comparison between categorical data (number (%)) was performed using Chi square test. Comparison between values of different variables in the two studied groups was performed using either unpaired t test or Mann-Whitney test whenever it was appropriate. Correlation between sleep parameters and different parameters in patient group was performed using either Pearson or Spearman's Rank correlation coefficient. SPSS computer program (version 19 windows) was used for data analysis. P value ≤ 0.05 was considered significant.

3. Results

3.1. Demographic Data

VaD patients and control group showed similar demographic profiles (Table 1). There were with no statistical significant difference as regards age or sex between both groups. But there was statistical significant difference between both groups regarding body mass index (BMI) with high BMI in the VaD group.

Table 1. Demographic features in the two studied groups.

	VaD group (n = 20)	Control (n = 20)	P value
Age (yrs.)			
Min.-maximum	62.0 - 69.0	61.0 - 69.0	
Mean \pm SD	66.05 \pm 2.04	65.25 \pm 2.22	0.243
Sex			
Female	10 (50%)	10 (50%)	1.000
Male	10 (50%)	10 (50%)	
BMI			
Min.-maximum	19.7 - 26.8	19.5 - 25.0	
Mean \pm SD	23.81 \pm 2.32	22.29 \pm 1.69	0.026*

There was statistical significant difference between VaD group and control group regarding hypertension and hyperlipidemia. Sleep disorders were present in 20 patients (100%) in VaD group, but only in 5 (25%) patients in control group. The sleep disorders were insomnia in 3 (15%) patients, excessive daytime sleepiness EDS in 13 (65%) patients, sleep disordered breathing (SDB) in 10 (50%) patients, REM behavioral disordered (RBD) in one (5%) patient and rest-less leg syndrome RLS & PLM in 3 (15%) patients.

As regards activities of Daily Living (ADL) there was statistical significant difference between VaD group and control group, most of VaD patients had low ADL. There was statistical significant difference between VaD group and control group regarding CDR (**Table 2**).

There was a statistical significant difference between VaD group and control group regarding MMSE (**Table 3**).

For the MRI brain findings in VaD group; there were large cortical infarction in 10 (50%) patients, subcortical infarction in 6 (30%) patients, lacunar infarcts in 9 (45%) patients, diffuse white matter hyperintensities in 12 (60%) patients and brain atrophy in 20 (100%) patients.

3.2. Subjective Sleep Assessment

There was a statistical significant difference between VaD group and control group regarding ESS and PSQI between both groups with higher results among patient group (**Table 4**).

There was a statistical significant correlation between CDR & MMSE and PSQI (the more severe the cognitive impairment, the poorer sleep quality). But, there was no statistical significant correlation between CDR & MMSE and ESS (no relation between degree of cognitive impairment and excessive daytime sleepiness) (**Table 5**).

3.3. Polysomnography Results

As regards sleep efficiency and continuity, the results showed poorer sleep efficiency,

Table 2. Clinical dementia rating scale (CDR) in the studied groups.

CDR	VaD group (n = 20)	Control (n = 20)	P value
0	0 (0.0%)	20 (100.0%)	
1	5 (25.0%)	0 (0.0%)	0.001*
2	15 (75.0%)	0 (0.0%)	

Table 3. MMSE in the studied groups.

MMSE	VaD group (n = 20)	Control (n = 20)	P value
Normal	0 (0.0%)	20 (100.0%)	
Mild	5 (25.0%)	0 (0.0%)	0.001*
Moderate	15 (75.0%)	0 (0.0%)	

Table 4. ESS & PSQI in the two studied groups.

ESS	VaD group (n = 20)	Control (n = 20)	P value
0 - 5	0 (0.0%)	18 (90.0%)	
6 - 10	7 (35.0%)	2 (10.0%)	
11 - 12	5 (25.0%)	0 (0.0%)	0.001*
13 - 15	4 (20.0%)	0 (0.0%)	
16 - 24	4 (20.0%)	0 (0.0%)	
PSQI	VaD group (n = 20)	Control (n = 20)	P value
<5	0 (0.0%)	20 (100.0%)	
>5	20 (100.0%)	0 (0.0%)	0.001*

Table 5. Correlation between severity of the disease and subjective sleep assessment.

Sleep parameters	ESS		PSQI	
	Correlation coefficient	P value	Correlation coefficient	P value
CDR	-0.187	0.430	0.579	0.007*
MMSE	-0.187	0.430	0.579	0.007*

prolonged SL, and a tendency for more wake after sleep onset (AI) in patient group. As regards Hypnogram, the results showed that VaD patients spent more time in stage I and II sleep, but had lower percentage of SWS and REM sleep compared to control group. As regards REM parameters the results showed VaD patients had lower percentage of REM sleep, delayed REML and decreased 1st REMD compared to control group. As regards Sleep fragmentation parameters, the results showed that VaD patients had short TST, more WASO (more time sent awake) and high SFI (more sleep stage shifts) compared to control group. As regards respiratory events; VaD patients had more Apnea, Hypopnea, RDI and high SpO₂ desaturation compared to control group. Finally, as regards PLMS there was a statistical significant increase of PLMS with RLS in VaD group in comparison to control groups (**Table 6**).

As regard Sleep parameters in the VaD group in correlation to ADL scores, there were statistical significant negative correlation between AI & RDI and ADL ; high AI & RDI is associated with low ADL (more functional impairment), but there was no statistical significance for Sleep efficiency (**Table 7**).

There were statistical significant difference for Apnea, RDI & SPO₂ and BMI score (more Apnea/H and RDI with high BMI index and more average SpO₂ desaturation with high BMI), but not for SE and AI (**Table 8**).

There was no statistical significant difference as regards sleep parameters (SE, SL, SWS and AI), grade of dementia (MMSE and CDR) and subjective sleep assessment (PSQI) in patient group (**Table 9**).

There was statistical significant difference for SE, AI, Apnea, RDI & SPO₂ with the ESS score severity. Also, there was statistical significant difference for BMI in comparison to ESS score severity; severe ESS score with high BMI (**Table 10**).

Table 6. Polysomnography results in the two studied groups.

	VaD group (n = 20)	Control (n = 20)	P value [#]
SE	67.49 ± 18.69	88.10 ± 4.40	0.001*
SL	18.70 ± 13.22	18.60 ± 5.13	0.850
Arousal I	13.44 ± 12.27	1.66 ± 0.92	0.001*
I	47.96 ± 22.68	4.40 ± 1.13	0.001*
II	48.99 ± 22.01	50.22 ± 0.90	0.351
SWS	1.35 ± 4.80	21.52 ± 1.04	0.001*
REM	1.47 ± 2.45	23.80 ± 0.92	0.001*
REML	82.90 ± 92.87	65.10 ± 4.55	0.397
First REMD	1.65 ± 2.18	18.38 ± 0.30	0.001*
TST	166.49 ± 57.99	281.85 ± 36.95	0.001*
WASO	57.52 ± 33.87	16.12 ± 5.83	0.001*
SFI	0.51 ± 0.25	0.39 ± 0.09	0.046*
Apnea/H	15.51 ± 24.89	0.60 ± 0.81	0.173
Hypopnea/H	4.13 ± 6.33	0.22 ± 0.34	0.018*
RDI	21.62 ± 28.31	0.82 ± 1.10	0.013*
SPO2	6.10 ± 12.70	0.12 ± 0.21	0.049*
PLMs	4.94 ± 8.26	1.15 ± 0.44	0.027*

Table 7. Correlation between sleep parameters in the patient group and ADL.

Sleep parameters	ADL	
	Correlation coefficient	P value
SE	-0.420	0.065
Arousal I	-0.541	0.014*
RDI	-0.791	0.001*

Table 8. Sleep parameters in the patient group classified according to BMI subgroups.

	BMI < 25 (n = 13)	BMI > 25 (n = 7)	P value [#]
SE	67.21 ± 18.14	68.03 ± 21.16	0.968
Arousal I	12.02 ± 13.68	16.09 ± 9.49	0.143
Apnea/H	10.65 ± 28.64	24.54 ± 13.23	0.014*
RDI	14.77 ± 29.31	34.33 ± 23.00	0.047*
SPO2	1.23 ± 2.42	15.14 ± 18.77	0.004*

There were no significant correlation between sleep parameters and MRI findings; either subjective sleep assessment; ESS & PSQI or objective PSG parameters; SE, SL, AI, RDI & SPO2, WASO and SFI. The MRI findings were; the presence of cortical or subcortical infarction, frontal, thalamic or lacunar infarction, different types of diffuse white matter hyperintensities, degree of brain atrophy and side of infarction; left, right or bilateral (**Table 11** & **Table 12**).

Table 9. Correlation between sleep parameters and grade of dementia (MMSE and CDR) and PSQI in patient group.

	MMSE		CDR		PSQI	
	Pearson correlation	P value	Spearman's correlation	P value	Pearson correlation	P value
SE	0.049	0.837	0.170	0.473	-0.030	0.901
SL	-0.115	0.628	-0.049	0.839	0.193	0.415
SWS	0.135	0.570	0.328	0.158	-0.227	0.336
Arousal index	0.147	0.536	-0.183	0.440	0.120	0.613

Table 10. Correlation between sleep parameters and ESS score severity (normal, mild, moderate, severe).

Sleep parameters	ESS	
	Correlation coefficient	P value
SE	0.511	0.021*
Arousal I	0.578	0.008*
Apnea	0.900	0.001*
RDI	0.854	0.001*
SPO2	0.810	0.001*
BMI	0.674	0.001*

Table 11. Correlation between sleep parameters and site of lesion.

	Large cortical infraction (n = 10)	Subcortical infraction (n = 6)	P value ^f
SE	67.68 ± 24.09	63.87 ± 12.35	0.550
SL	22.55 ± 15.95	24.33 ± 8.43	0.957
Arousal I	13.29 ± 15.66	12.73 ± 5.88	0.515
RDI	21.02 ± 33.50	9.30 ± 11.75	0.743
SPO2	7.10 ± 16.39	4.50 ± 11.02	0.428
WASO	53.15 ± 35.79	61.92 ± 38.17	0.664
SFI	0.43 ± 0.24	0.37 ± 0.12	0.703
PSQI	11.70 ± 2.16	10.83 ± 2.04	0.432
ESS	11.70 ± 3.20	11.67 ± 3.33	0.956
	Frontal (n = 6)	Thalamic (n = 9)	P value
SE	77.35 ± 19.17	65.03 ± 18.27	0.216
SL	16.83 ± 16.71	18.78 ± 14.20	0.679
Arousal I	18.53 ± 18.78	11.10 ± 9.63	0.443
SFI	0.51 ± 0.27	0.59 ± 0.27	0.516
SWS	0.43 ± 1.06	2.71 ± 7.08	0.674
REM	1.30 ± 1.77	0.89 ± 2.10	0.306
ESS	12.00 ± 3.95	11.78 ± 2.95	1.000
PSQI	12.17 ± 2.04	11.33 ± 1.73	0.369

Table 12. Correlation between sleep parameters and type of diffuse white matter hyperintensities, degree of brain atrophy and side of the lesion.

Sleep parameters	Type of diffuse white matter hyperintensities			P value
	Correlation coefficient			
SE	-0.023			0.944
SL	-0.291			0.359
Arousal I	0.496			0.101
RDI	0.321			0.310
SPO2	0.090			0.782
WASO	0.420			0.174
SFI	0.359			0.252
PSQI	-0.169			0.600
ESS	-0.043			0.895
BMI	0.460			0.132
Sleep parameters	Degree of brain atrophy			P value
	Correlation coefficient			
SE	-0.288			0.219
SL	-0.174			0.462
Arousal I	0.392			0.087
RDI	0.236			0.316
SPO2	0.201			0.397
WASO	0.305			0.191
SFI	0.00			1.000
PSQI	-0.062			0.795
EES	0.035			0.882
Apnea	0.333			0.151
BMI	0.323			0.165
	Right (n = 8)	Left (n = 4)	Bilateral (n = 8)	P value
SE	64.10 ± 21.30	58.38 ± 27.63	75.45 ± 5.89	0.275
SL	23.50 ± 14.87	15.62 ± 14.99	15.44 ± 10.65	0.443
Arousal I	11.19 ± 7.81	26.12 ± 20.93	9.35 ± 6.58	0.222
RDI	16.00 ± 17.07	36.22 ± 48.62	19.92 ± 26.63	0.872
SPO2	10.88 ± 19.42	3.25 ± 3.77	2.75 ± 3.33	0.967
WASO	61.88 ± 34.98	80.38 ± 50.79	41.75 ± 13.43	0.317
SFI	0.46 ± 0.26	0.50 ± 0.34	0.57 ± 0.22	0.466
PSQI	11.12 ± 1.89	13.00 ± 1.63	11.12 ± 1.81	0.223
ESS	11.62 ± 3.46	12.25 ± 2.06	11.62 ± 3.11	0.847

4. Discussion

Sleep is considered to be important for cognitive function, cognitive deficits and sleep disorders are influenced by one another [21]. Given the rising prevalence of cerebrovascular diseases and dementia with aging, the development of more sensitive neuropsychological and neuroimaging diagnostic and prognostic tools, will be crucial for elucidating and modifying VCI pathophysiology to develop new modes of intervention for disease prevention and treatment.

The present study revealed significant correlation for Apnea, RDI & SPO₂ with BMI; more Apnea and RDI with high BMI and more average SpO₂ desaturation with high BMI.

Hypertension was present in 80% of VaD patients in this study. These findings denote the importance of hypertension as risk factors for vascular dementia. This fact was supported by the report of Hebert *et al.* (2000) [22]. Also, hyperlipidemia was present in 80% and cardiac diseases in 60% of VaD patients. Diabetes mellitus (DM) was present in 50% of VaD patients in this study. The association between dementia and DM can be explained through the effect of DM on cerebral blood flow especially with regards to reactivity and autoregulation or serving as a risk factor for clinically overt and silent brain insults.

In this study, the most common sleep complaints among VaD patients were; EDS (65%), SDB (50%), insomnia (15%) and RLS & PLMS (15%) and RBD (5%) respectively. These results were in accordance with that of Ramirez-Santos *et al.* (2015) who stated that in mild cognitive impairment and dementia in general (regardless of type) are associated with a marked increase in sleep-related complaints [23]. The global prevalence reported for any sleep disorder was 82%, for insomnia 37.1%, for hypersomnia 47.8%, for parasomnia 21.4% and apnea 54.5%. Also, Guarnieri *et al.* (2012) found that VaD patients had a higher frequency of sleep disturbance (insomnia, EDS, SDB, RBD & RLS) than that observed in AD patients [24]. The highest risk increase with respect to AD was for SDB with the high frequency of obstructive sleep apnea (OSA) reported in stroke patients. Both the vascular damage and SDB have some common risk factors such as excessive BMI and hypertension [25].

In this study, there was a statistical significant correlation between CDR & MMSE and PSQI; the more severe the cognitive impairment, the poorer sleep quality which explain the high prevalence of SDB, insomnia, RLS & PLMS and RBD in VaD patients. Similar findings were reported by Mondal *et al.* (2013) who found that an abnormal ESS were more likely to have an abnormal PSQI score [26]. But, the results of this study showed no statistical significant correlation between CDR & MMSE and ESS; no relation between grade of cognitive impairment and degree of excessive daytime sleepiness which means that EDS can be found in the earliest stage of vascular dementia. Similar findings were reported by Miu, Szeto (2012) who found no correlation between MMSE and ESS among 105 of mild to moderate dementia patients [27]. Furthermore, Merilino *et al.* (2010) who showed that, although insomnia represented the most common

sleep disturbance in 750 subjects aged 65 years or older, 86 of them were diagnosed as demented, and this was not associated with cognitive impairment [28]. However, the severity of SPO2 desaturation, was associated with high ESS; excessive daytime sleepiness and also those with an abnormal ESS had higher BMI and higher AHI.

Taken together, the data suggests that SE and continuity was poorer in patients with VaD in this study, as the sleep-wake cycle is regulated by a complex interplay of mechanisms located mainly in the brainstem, hypothalamus, and thalamus [29]. And any lesion such as an acute stroke, which directly affects the thalamocortical network function has the potential to disrupt the sleep-wake cycle and lead to sleep disturbances [30]. As lesions of the cortex might compromise this process with abnormal deactivation of frontal and thalamic areas from presleep wakefulness to non-REM sleep and hence primarily affect sleep continuity [31].

In the present study there was a significant negative correlation between AI & RDI and ADL and significant correlation for SE, AI & RDI with the ESS score severity. Similar results were reported by Jiang *et al.* (2013) as they found that patients with vascular cognitive impairment-no dementia had higher PSQI scores compared with controls [9]. Compared with controls, patients had reduced TST, decreased SWS and REM sleep, longer SL, lower SE, and increased AI and PLMS index.

The present study was guided by the idea that REM sleep parameters may reflect different pathophysiological mechanisms between AD and VaD.

As, cholinergic neurons are important determinants of REM sleep, with cholinergic activity low during SWS and high during REM sleep [32]. Stroke causes a central imbalance of neurotransmitters, such as acetylcholine, serotonin, and melatonin, causing sleep structure abnormalities [33]. A similar REM parameter dysfunction was present in AD; reduced REM duration, and increased first REM episode [34]. But, this can be explained because of the dependence of REM sleep on the integrity of cholinergic neurotransmission and the widespread deterioration of cholinergic systems throughout the basal forebrain in AD [35].

The present study revealed a positive significant correlation between ESS, Apnea, RDI & SPO2 and BMI score. Similar findings were reported by Bassetti *et al.* (2006), as they found a significant correlation between apnea-hypopnea index and BMI [36]. Also, Erkinjuntti *et al.* (1987) reported that patients with multi-infarct dementia tended to have more apneas/hypopneas than those with AD, and apneas/hypopneas tended to increase in direct proportion to the severity of dementia [37]. However, Karaca (2016) found no correlation between BMI and sleep quality (PSQI) [38]. This discrepancy may result from differences in evaluation methods; subjective and/or PSG, and differences in the patients' age range.

Circadian rhythm disturbances are common in patients with dementia and affect more than 80 % of those over age 65, resulting in insomnia, excessive daytime sleepiness, and day/night reversal [39]. Similar to the present study, Guarneri *et al.* (2012) found that VD patients had disrupted sleep-wake cycles asso-

ciated with shorter sleep periods and lower sleep quality which were more significant than those in AD patients [24]. Both the degradation of sleep quality and the disintegration of the sleep-wake cycle in VaD may reflect the disruptive effects of the vascular lesions on the neural network dedicated to sleep regulation. Since most of the lacunes in VaD are located predominately in the internal capsule, basal ganglia, and the periventricular white matter. These lesions could disconnect the pathways leading to and from the suprachiasmatic nucleus, which might be involved in the regulation of the circadian sleep-wake cycle. Furthermore, stroke lesions may alter other circadian functions such as sleep-related secretion of growth hormone and melatonin [40].

Post stroke hypersomnia or EDS is due to reduced arousal because of lesions involving the ascending arousal pathways. This occurs in patients with bilateral lesions of the thalamus, subthalamic and hypothalamic area, tegmental mid-brain, and pons, where fibers of the ascending arousal pathways can be severely injured even by single small lesions [41]. White matter hyperintensities (WMHs) severity was significantly associated with sleep disturbance, with most symptoms related to daytime hypersomnolence and restless sleep. This finding might be explained by disruption of the frontal-subcortical neuronal circuits and basal ganglia [42]. Baillet *et al.* (2017) found that a higher sleep fragmentation was associated with a reduction in white matter integrity due to WMHs [43]. Also, greater sleep fragmentation was associated with more severe arteriolosclerosis and subcortical infarcts in brain autopsies in community-dwelling older people [44].

Strokes related insomnia are associated with caudate or subcortical, thalamic and brainstem (thalamo-mesencephalic, pontomesencephalic, and pontine tegmentum) lesions. Patients may presented by inversion of the sleep-wake cycle with insomnia, night-time agitation, and daytime hypersomnia [45].

Researchers have been unable to link SDB frequency, type, or severity to the location of the stroke, however autonomic networks responsible for respiratory control may be disrupted with lesions in forebrain structures that control respiration as part of integrated behaviors such as speech or exercise [46]. Hemispheric strokes in the frontal cortex, basal ganglia, or internal capsule may cause respiratory apraxia, with impaired voluntary modulation of breathing amplitude and frequency, leaving patients unable to take a deep breath or hold the breath [47]. Also, the medulla may be less responsive to rising Pco₂ levels during sleep [48]. SDB includes; OSA, central and mixed apnea; is linked with white matter disease on magnetic resonance imaging and silent strokes [49]. SDB patients are at a higher risk of developing cognitive impairment or incident AD [50] [51].

OSA is a common feature of vascular dementia, and leads to fragmented sleep, increased nocturnal confusion, and excessive daytime sleepiness [52]. In the acute post-stroke period, there is a high prevalence of central apneas, which typically resolve [53]. Central sleep apnea and Cheyne-Stokes respiration is caused by motor dysfunction that lead to destabilization of the upper airways due to involvement of pyramidal-related musculature without affecting swallowing and cause a higher instability of the upper respiratory tract during the night [54].

Post stroke PLMS may be of primary type; is not always associated with sleep disturbance, and may be due to unilateral hemispheric, pontine base or tegmentum and spinal strokes [55]. But, patients with bilateral RLS had lesions in both the corona radiata and basal ganglia, whereas patients with lesions only in the corona radiata had either contralateral or bilateral RLS [56]. Most commonly, RLS was accompanied by PLMS in sleep [47]. A common mechanism behind both PLM and RLS might be due to dysfunction of the dopaminergic system, possibly on the level of either pre- and/or post-synaptic striatal and/or spinal dopamine receptors [57]. Evidence supporting an association between wandering in dementia and RLS and/or PLMS; as neuroimaging studies have suggested reduced dopamine reuptake in the caudate and putamen among AD patients who wander relative to those who did not [58].

Cases of stroke have been described in association with RBD include lesions in the pontine tegmentum, midbrain, or paramedian thalamus which may trigger visual hallucinations, especially at sleep onset [59]. Thalamus, temporal, parietal, and occipital lobes strokes may lead to increased dreaming and nightmares and/or a syndrome of dream-reality confusion [60]. Patients with strokes in the pons, midbrain, or paramedian thalamus may experience peduncular hallucinosis which characterized by complex, colorful, dreamlike visual hallucinations, especially in the evening and at sleep onset. Peduncular hallucinosis may represent a release of REM sleep mentation and may be associated with insomnia [45].

In this study there were no significant correlation between MRI findings (the presence of cortical or subcortical infarction, frontal, thalamic or lacunar infarction, different types of diffuse white matter hyperintensities, degree of brain atrophy and side of infarction; left, right or bilateral) and sleep parameters (subjective sleep assessment; ESS & PSQI or PSG parameters; SE, SL, AI, RDI & SPO2, WASO and SFI) and this might be due to associated widespread injury and dysfunction throughout the brain in cases of stroke [61]. Similar findings were reported by Karaca (2016) who reported that there was no significant correlation between right-left cerebral involvement and sleep quality [38]. Lutsey *et al.* (2016) found that neither OSA nor abnormal sleep duration were statistically significantly associated with cerebral infarcts, white matter brain volumes or regional brain volumes by MRI imaging in VaD and AD patients [62].

However, some studies suggest that right-sided strokes decrease REM and REM density, while left-sided strokes decrease NREM stages. Körner *et al.* [63] found that slow-wave sleep was decreased in infarctions of the left hemisphere stroke patients. While Pasic *et al.* (2011) and Da Rocha *et al.* (2013) reported that the involvement of the right cerebral hemisphere is more frequent in patients with post stroke sleep disorder; insomnia, fragmented sleep, difficulty in falling asleep, greater sleep latency and worse subjective sleep quality [64] [65]. Also, Wu *et al.* (2016) found that patients with minor thalamic lesions are at increased risk for sleep disturbance, sleep-related breathing disorders, and memory deficits [66]. In this respect, the results are contradictory, and further studies with large number are needed.

The available data confirms that sleep is significantly impaired in patients with VaD at both subjective level and the objective by PSG recordings which may be used as a surrogate marker of vascular dementia.

Much evidence suggests that daytime sleepiness, sleep disturbances, or SDB are associated with an increased risk for vascular dementia, ischemic stroke, hypertension, and heart disease [67]. As sleep disorders are frequent and can have serious consequences on patient's health and quality of life and some sleep disorders are more challenging to treat, most can be easily managed with adequate interventions.

Simple questions of the patient or bed-partner for the symptoms and signs of the OSA, such as loud snoring, observed apneas, and daytime sleepiness, would help identify those in need of further diagnostic evaluation as OSA which is a treatable disorder [68]. A careful clinical evaluation of sleep disorders should be performed routinely in the clinical setting of persons with cognitive decline. Instrumental assessment; PSG should be used in selected patients.

5. Limitations and Strengths

This study has some limitations which have to be taken into consideration. First, the sample size was relatively small, resulting in low statistical power for detecting significant differences between groups. Second, the difficulty of doing second PSG to confirm results and any day to day variation of sleep disturbances. Third, the sample lack different stages of VaD, as severe cases were excluded from the study.

Despite these limitations this work is unique in that: 1) used an extensive clinical evaluation including a combination of neurological examinations and a detailed neuropsychological tests in order to define the cognitive status of each participant; 2) assessment of sleep disorders by means of subjective and objective instruments as, PSG is essential for a correct diagnosis of some sleep disturbances like SDB and measures sleep architecture; 3) state-of-the-art brain MRI assessment was used and; 4) provide insights into sleep disturbances in VaD patients and highlights the importance of this frequently missed aspect in the care of dementia patients and their caregivers.

6. Conclusions

The information provided in this study helps provide insights into the importance of sleep disturbance in vascular dementia patients and highlights the importance of this frequently missed aspect in the care of dementia patients and their caregivers. Sleep disorders can be detected in early stages of VaD.

The most common sleep complaints among VaD patients were EDS, SDB, insomnia and RLS & PLMS and RBD respectively. The more severe the cognitive impairment (MMSE & CDR), the poorer the sleep quality (PSQI) which explains the high prevalence of SDB, insomnia, RLS & PLMS and REM behavioral disorder in VaD patients.

PSG study of VaD patients showed poorer SE, prolonged SL and high AI. Also, VaD patients spend more time in stage I, less time in SWS and REM sleep, together with delayed REML, and less 1st REML. Another PSG findings, increased sleep fragmentation (more WASO & SFI) and increased AI and PLMS index. VaD patients had significant high Apnea, Hypopnea & RDI score with high average SPO2 desaturation. Early detection and treatment of SDB in these cases may be of utmost importance and may prevent further cognitive decline.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Helman, A.M. and Murphy, P.M. (2016) Vascular Cognitive Impairment: Modeling a Critical Neurologic Disease *in Vitro* and *in Vivo*. *Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease*, **1862**, 975-982. <https://doi.org/10.1016/j.bbadis.2015.12.009>
- [2] Ganguli, M. (2011) Epidemiology of Dementia. In: Abou-Saleh, M.T., Katona, C. and Kumar, A., Eds., *Principles and Practice of Geriatric Psychiatry*, 3rd Edition, Wiley, Hoboken, NJ, 207-212. <https://doi.org/10.1002/9780470669600.ch38>
- [3] Azarpazhooh, M.R., Avan, A., Cipriano, L.E., Munoz, D.G., Sposatoa, L.A. and Hachinski, V. (2018) Concomitant Vascular and Neurodegenerative Pathologies Double the Risk of Dementia. *Alzheimer's & Dementia*, **14**, 148-156. <https://doi.org/10.1016/j.jalz.2017.07.755>
- [4] Elshahidi, M.H., Elhadidi, M.A., Sharaq, A., Mostafa, A. and Elzhery, M.A. (2017) Prevalence of Dementia in Egypt: A Systematic Review. *Neuropsychiatric Disease and Treatment*, **13**, 715-720. <https://doi.org/10.2147/NDT.S127605>
- [5] Hu, G.C. and Chen, M.Y. (2017) Post-Stroke Dementia: Epidemiology, Mechanisms and Management. *International Journal of Gerontology*, **11**, 210-214. <https://doi.org/10.1016/j.ijge.2017.07.004>
- [6] Gehrman, P., Gooneratne, N.S., Brewster, G.S., *et al.* (2017) Impact of Alzheimer Disease Patients' Sleep Disturbances on Their Caregivers. *Geriatric Nursing*, **39**, 60-65. <https://doi.org/10.1016/j.gerinurse.2017.06.003>
- [7] Chiu, P.Y., Liu, C.-H. and Tsai, C.-H. (2007) Neuropsychiatric Manifestations in Vascular Cognitive Impairment Patients with and without Dementia. *Acta Neurologica Taiwanica*, **16**, 86-91.
- [8] Biessels, G.J. (2016) Diagnosis and Treatment of Vascular Damage in Dementia. *Biochimica et Biophysica Acta*, **1862**, 869-877. <https://doi.org/10.1016/j.bbadis.2015.11.009>
- [9] Jiang, B., Ding, C.-Y., Yao, G., Yao, C.-S., Zhang, Y.-Y., Ge, J.-L., *et al.* (2013) Polysomnographic Abnormalities in Patients with Vascular Cognitive Impairment-No dementia. *Sleep Medicine*, **14**, 1071-1075. <https://doi.org/10.1016/j.sleep.2013.07.003>
- [10] Rakesh, G., Szabo, S.T., Alexopoulos, G.S. and Zannas, A.S. (2017) Strategies for Dementia Prevention: Latest Evidence and Implications. *Therapeutic Advances in Chronic Disease*, **8**, 121-136. <https://doi.org/10.1177/2040622317712442>
- [11] American Psychiatric Association (2013) Diagnostic and Statistical Manual of

- Mental Disorders. 5th Edition, American Psychiatric Association, Washington DC. <https://doi.org/10.1176/appi.books.9780890425596>
- [12] Morris, J.C. (1993) The Clinical Dementia Rating (CDR): Current Version and Scoring Rules. *Neurology*, **43**, 2412-2414. <https://doi.org/10.1212/WNL.43.11.2412-a>
- [13] Folstein, M.F., Folstein, S.E. and McHugh, P.R. (1975) "Mini-Mental State": A Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research*, **12**, 189-198. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
- [14] Alexopoulos, G.S., Abrams, R.C., Young, R.C. and Shamoian, C.A. (1988) Use of the Cornell Scale in Nondemented Patients. *Journal of the American Geriatrics Society*, **36**, 230-236. <https://doi.org/10.1111/j.1532-5415.1988.tb01806.x>
- [15] Taylor, J.A. (1953) A Personality Scale of Manifest Anxiety. *The Journal of Abnormal and Social Psychology*, **48**, 285-290. <https://doi.org/10.1037/h0056264>
- [16] Assad, T. and Kahla, O. (2001) Psychometric Sleep Assessment Instruments: An Arabic Version for Sleep Evaluation. Elnahda, El-Fagala, Egypt, 26-47.
- [17] Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R. and Kupfer, D.J. (1989) The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research. *Psychiatry Research*, **28**, 193-213. [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4)
- [18] Johns, M.W. (1991) A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. *Sleep*, **14**, 540-545. <https://doi.org/10.1093/sleep/14.6.540>
- [19] Mellman, T.A., Bustamante, V., Fins, A.I., Pigeon, W.R. and Nolan, B. (2002) REM Sleep and the Early Development of Posttraumatic Stress Disorder. *The American Journal of Psychiatry*, **159**, 1696-1701. <https://doi.org/10.1176/appi.ajp.159.10.1696>
- [20] Hori, T., Yoshio, S., Einosuke, K., et al. (2001) A Proposed Supplements and Amendments to "A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects", the Rechtschaffen & Kales (1968) Standard. *Psychiatry and Clinical Neurosciences*, **55**, 305-310. <https://doi.org/10.1046/j.1440-1819.2001.00810.x>
- [21] Bliwise, D.L., Mercaldo, N.D., Avidan, A.Y., Boeve, B.F., Greer, S.A. and Kukull, W.A. (2011) Sleep Disturbance in Dementia with Lewy Bodies and Alzheimer's Disease: A Multicenter Analysis. *Dementia and Geriatric Cognitive Disorders*, **31**, 239-246. <https://doi.org/10.1159/000326238>
- [22] Hébert, R., Lindsay, J., Verreault, R., Rockwood, K., Hill, G. and Dubois, M.F. (2000) Vascular Dementia Incidence and Risk Factors in the Canadian Study of Health and Aging. *Stroke*, **31**, 1487-1493. <https://doi.org/10.1161/01.STR.31.7.1487>
- [23] Ramirez-Santos, R., Acosta-Castillo, G. and Sosa-Ortiz, A. (2015) Sleep Disorders Prevalence among Patients with Mild Cognitive Impairment and Dementia Subtypes. *Alzheimer's & Dementia*, **11**, 394. <https://doi.org/10.1016/j.jalz.2015.06.334>
- [24] Guarnieri, B., Adorni, F., Musicco, M., Appollonio, I., Bonanni, E., Caffarra, P., et al. (2012) Prevalence of Sleep Disturbances in Mild Cognitive Impairment and Dementing Disorders: A Multicenter Italian Clinical Cross-Sectional Study on 431 Patients. *Dementia and Geriatric Cognitive Disorders*, **33**, 50-58. <https://doi.org/10.1159/000335363>
- [25] Hermann, D.M. and Bassetti, C.L. (2009) Sleep-Related Breathing and Sleep-Wake Disturbances in Ischemic Stroke. *Neurology*, **73**, 1313-1322. <https://doi.org/10.1212/WNL.0b013e3181bd137c>
- [26] Mondal, P., Gjevre, J.A., Taylor-Gjevre, R. and Lim, H.J. (2013) Relationship be-

- tween the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in a Sleep Laboratory Referral Population. *Nature and Science of Sleep*, **5**, 15-21. <https://doi.org/10.2147/NSS.S40608>
- [27] Miu, D.K. and Szeto, S.S. (2012) Sleep Disturbances among a Group of Dementia Participants. *Journal of Clinical Gerontology and Geriatrics*, **3**, 105-109. <https://doi.org/10.1016/j.jcgg.2012.04.008>
- [28] Merlino, G., Piani, A., Gigli, G.L., Cancelli, I., Rinaldi, A., Baroselli, A., Serafini, A., Zanchettin, B. and Valente, M. (2010) Daytime Sleepiness Is Associated with Dementia and Cognitive Decline in Older Italian Adults: A Population-Based Study. *Sleep Medicine*, **11**, 372-377. <https://doi.org/10.1016/j.sleep.2009.07.018>
- [29] Gent, T., Bassetti, C.L. and Adamantidis, A.R. (2018) Sleep-Wake Control and the Thalamus. *Current Opinion in Neurobiology*, **52**, 188-197. <https://doi.org/10.1016/j.conb.2018.08.002>
- [30] Lyons, O.D. and Ryan, C.M. (2015) Sleep Apnea and Stroke. *Canadian Journal of Cardiology*, **31**, 918-927. <https://doi.org/10.1016/j.cjca.2015.03.014>
- [31] Weiner, O.M. and Dang-Vu, T.T. (2016) Spindle Oscillations in Sleep Disorders: A Systematic Review. *Neural Plasticity*, **2016**, Article ID: 7328725. <https://doi.org/10.1155/2016/7328725>
- [32] Pase, M.P., Himali, J.J., Grima, N.A., Beiser, A.S., Satizabal, C.L., *et al.* (2017) Sleep Architecture and the Risk of Incident Dementia in the Community. *Neurology*, **89**, 1244-1250. <https://doi.org/10.1212/WNL.0000000000004373>
- [33] Bassetti, C.L. and Hermann, D.M. (2011) Chapter 62: Sleep and Stroke. *Handbook of Clinical Neurology*, **99**, 1051-1072. <https://doi.org/10.1016/B978-0-444-52007-4.00021-7>
- [34] Assad, T., Sweed, H., Alloush, A., Shaheen, A. and Hamdy, M. (2017) Sleep Profile in Patients with Alzheimer's Disease: A Polysomnographic Evaluation in an Egyptian Sample. *Sleep Medicine*, **40**, e19. <https://doi.org/10.1016/j.sleep.2017.11.048>
- [35] Rauchs, G., Schabus, M., Parapatics, S., *et al.* (2008) Is There a Link between Sleep Changes and Memory in Alzheimer's Disease? *Neuroreport*, **19**, 1159-1162. <https://doi.org/10.1097/WNR.0b013e32830867c4>
- [36] Bassetti, C.L., Milanova, M. and Gugger, M. (2006) Sleep-Disordered Breathing and Acute Ischemic Stroke: Diagnosis, Risk Factors, Treatment, Evolution, and Long-Term Clinical Outcome. *Stroke*, **37**, 967-972. <https://doi.org/10.1161/01.STR.0000208215.49243.c3>
- [37] Erkinjuntti, T., Partinen, M., Sulkava, R., Telakivi, T., Salmi, T. and Tilvis, R. (1987) Sleep Apnea in Multi-Infarct Dementia and Alzheimer's Disease. *Sleep*, **10**, 419-425. <https://doi.org/10.1093/sleep/10.5.419>
- [38] Karaca, B. (2016) Factors Affecting Poststroke Sleep Disorders. *Journal of Stroke and Cerebrovascular Diseases*, **25**, 727-732. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.11.015>
- [39] Sullivan, S.C. and Richards, K.C. (2004) Predictors of Circadian Sleep-Wake Rhythm Maintenance in Elders with Dementia. *Aging & Mental Health*, **8**, 143-152. <https://doi.org/10.1080/13607860410001649608>
- [40] Siccoli, M., Valko, P.O., Hermann, D.M. and Bassetti, C.L. (2008) Central Periodic Breathing in 74 Patients with Acute Ischemic Stroke—Neurogenic and Cardiogenic Factors. *Journal of Neurology*, **255**, 1687-1692. <https://doi.org/10.1007/s00415-008-0981-9>
- [41] Vock, J., Achermann, P., Bischof, M., Milanova, M., Muller, C., Nirkko, A., Roth, C.

- and Bassetti, C.L. (2002) Evolution of Sleep and Sleep EEG after Hemispheric Stroke. *Journal of Sleep Research*, **11**, 331-338. <https://doi.org/10.1046/j.1365-2869.2002.00316.x>
- [42] Cheng, C.Y., Tsai, C.-F., Wang, S.-J., Hsu, C.-Y. and Fuh, J.-L. (2013) Sleep Disturbance Correlates with White Matter Hyperintensity in Patients with Subcortical Ischemic Vascular Dementia. *Journal of Geriatric Psychiatry and Neurology*, **26**, 158-164. <https://doi.org/10.1177/0891988713493503>
- [43] Baillet, M., Dilharreguy, B., Pérès, K., Dartigues, J.-F., Mayo, W. and Catheline, G. (2017) Activity/Rest Cycle and Disturbances of Structural Backbone of Cerebral Networks in Aging. *NeuroImage*, **146**, 814-820. <https://doi.org/10.1016/j.neuroimage.2016.09.051>
- [44] Lim, A.S., Yu, L., Schneider, J.A., Bennett, D.A. and Buchman, A.S. (2016) Sleep Fragmentation, Cerebral Arteriosclerosis, and Brain Infarct Pathology in Community-Dwelling Older People. *Stroke*, **47**, 516-518. <https://doi.org/10.1161/STROKEAHA.115.011608>
- [45] Bassetti, C.L. (2017) Sleep and stroke. In: Kryger, M., Roth, T. and Dement, W., Eds., *Neurologic Disorders*, 6th Edition, Elsevier, Amsterdam, 903-915. <https://doi.org/10.1016/B978-0-323-24288-2.00093-3>
- [46] Sharma, S. and Culebras, A. (2016) Sleep Apnea and Stroke. *Stroke and Vascular Neurology*, **1**, 1-7. <https://doi.org/10.1136/svn-2016-000038>
- [47] Ferre, A., Ribo, M., Rodriguez-Luna, D., Romero, O., Sampol, G., Molina, C. and Álvarez-Sabin, J. (2013) Strokes and Their Relationship with Sleep and Sleep Disorders. *Neurologia*, **28**, 103-118. <https://doi.org/10.1016/j.nrl.2010.09.016>
- [48] Nogués, M.A. and Benarroch, E. (2008) Abnormalities of Respiratory Control and the Respiratory Motor Unit. *The Neurologist*, **14**, 273-288. <https://doi.org/10.1097/NRL.0b013e318173e830>
- [49] Kim, H., Yun, C.H., Thomas, R.J., et al. (2013) Obstructive Sleep Apnea as a Risk Factor for Cerebral White Matter in a Middle-Aged and Older General Population. *Sleep*, **36**, 709-715. <https://doi.org/10.5665/sleep.2632>
- [50] Liguori, C., Mercuri, N.B., Izzi, F., Romigi, A., Cordella, A., Sancesario, G. and Placidi, F. (2017) Obstructive Sleep Apnea Is Associated with Early but Possibly Modifiable Alzheimer's Disease Biomarkers Changes. *Sleep*, **40**, zsx011. <https://doi.org/10.1093/sleep/zsx011>
- [51] Lee, E., Wub, Y.S., Juna, J.Y., Kuka, K.S. and Honga, C.K. (2019) Sleep-Disordered Breathing and Alzheimer's Disease: A Nationwide Cohort Study. *Psychiatry Research*, **273**, 624-630. <https://doi.org/10.1016/j.psychres.2019.01.086>
- [52] McCarter, S.J., St. Louis, E.K. and Boeve, B.F. (2015) Sleep, Cognitive Dysfunction, and Dementia. In: Chokroverty, S. and Billiard, M., Eds., *Sleep Medicine*, Springer, New York. https://doi.org/10.1007/978-1-4939-2089-1_33
- [53] Ooms, S. and Ju, Y. (2016) Treatment of Sleep Disorders in Dementia. *Current Treatment Options in Neurology*, **18**, 40. <https://doi.org/10.1007/s11940-016-0424-3>
- [54] Bonnin-Vilaplana, M., Arboix, A., Parra, O., García-Eroles, L., Montserrat, J.M., Massons, J.M. and Massons, J. (2009) Sleep-Related Breathing Disorders in Acute Lacunar Stroke. *Journal of Neurology*, **256**, 2036. <https://doi.org/10.1007/s00415-009-5236-x>
- [55] Lee, S.J., Kim, J.S., Song, I.U., An, J.-Y., Kim, Y.-I. and Lee, K.-S. (2008) Poststroke Restless Legs Syndrome and Lesion Location: Anatomical Considerations. *Movement Disorders*, **24**, 77-84. <https://doi.org/10.1002/mds.22303>

- [56] Woo, H.G., Lee, D., Hwang, K.J. and Ahn, T.-B. (2017) Post-Stroke Restless Leg Syndrome and Periodic Limb Movements in Sleep. *Acta Neurologica Scandinavica*, **135**, 204-210. <https://doi.org/10.1111/ane.12582>
- [57] Manconi, M., Fanfulla, F., Ferri, R., Miano, S., *et al.* (2018) Periodic Limb Movements during Sleep in Stroke/TIA Prevalence, Course, and Cardiovascular Burden. *Neurology*, **90**, e1663-e1674. <https://doi.org/10.1212/WNL.0000000000005471>
- [58] Bliwise, D.L., Trotti, L.M., Yesavage, J.A. and Rye, D.B. (2012) Periodic Leg Movements in Sleep in Elderly Patients with Parkinsonism and Alzheimer's Disease. *European Journal of Neurology*, **19**, 918-923. <https://doi.org/10.1111/j.1468-1331.2012.03673.x>
- [59] Kimura, K., Tachibana, N., Kohyama, J., Otsuka, Y., Fukazawa, S. and Waki, R. (2000) A Discrete Pontine Ischemic Lesion Could Cause REM Sleep Behavior Disorder. *Neurology*, **55**, 894-895. <https://doi.org/10.1212/WNL.55.6.894>
- [60] Bassetti, C.L. (2005) Sleep and Stroke. *Seminars in Neurology*, **25**, 19-32. <https://doi.org/10.1055/s-2005-867073>
- [61] Dichgans, M. and Leys, D. (2017) Vascular Cognitive Impairment. *Circulation Research*, **120**, 573-591. <https://doi.org/10.1161/CIRCRESAHA.116.308426>
- [62] Lutsey, P., Norby, F., Gottesman, R., Mosley, T. and MacLehose, R. (2016) Sleep Apnea, Sleep Duration and Brain MRI Markers of Cerebral Vascular Disease and Alzheimer's Disease: The Atherosclerosis Risk in Communities Study (ARIC). *PLoS ONE*, **11**, e0158758. <https://doi.org/10.1371/journal.pone.0158758>
- [63] Korner, E., Flooh, E., Reinhart, B., Wolf, R., Ott, E., Krenn, W. and Lechner, H. (1986) Sleep Alterations in Ischemic Stroke. *European Neurology*, **25**, 104-110. <https://doi.org/10.1159/000116090>
- [64] Pasic, Z., Smajlovic, D., Dostovic, Z., Kojic, B. and Selmanovic, S. (2011) Incidence and Types of Sleep Disorders in Patients with Stroke. *Medical Archives*, **65**, 225-227. <https://doi.org/10.5455/medarh.2011.65.225-227>
- [65] Da Rocha, P.C., Barroso, M.T., Dantas, A.A.T.S.G., Melo, L.P. and Campos, T.F. (2013) Predictive Factors of Subjective Sleep Quality and Insomnia Complaint in Patients with Stroke: Implications for Clinical Practice. *Anais da Academia Brasileira de Ciências*, **85**, 1197-1206. <https://doi.org/10.1590/S0001-37652013005000053>
- [66] Wu, W., Cui, L., Fu, Y., Tian, Q., Liu, L. and Zhang, X. (2016) Sleep and Cognitive Abnormalities in Acute Minor Thalamic Infarction. *Neuroscience Bulletin*, **32**, 341-348. <https://doi.org/10.1007/s12264-016-0036-7>
- [67] Sindi, S., Kareholt, I., Johansson, L., *et al.* (2018) Sleep Disturbances and Dementia Risk: A Multicenter Study *Alzheimer's & Dementia*, **14**, 1235-1242. <https://doi.org/10.1016/j.jalz.2018.05.012>
- [68] Culebras, A. and Anwar, S. (2018) Sleep Apnea Is a Risk Factor for Stroke and Vascular Dementia. *Current Neurology and Neuroscience Reports*, **18**, 53. <https://doi.org/10.1007/s11910-018-0855-1>