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Original Article

Stroke patterns, topography and etiology in patients with obstructive sleep apnea-hypopnea syndrome

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Abstract: Objective: Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a risk factor for stroke. However, whether stroke type, topography, and etiology differ in OSAHS versus non-OSAHS individuals remains unclear. The role and features of OSAHS in stroke patients in China were investigated. Methods: We retrospectively analyzed 707 stroke patients from three medical centers in Shandong Province, China. Among these patients, 483 acute stroke cases were included, in which 233 had OSAHS. Gender, age, risk factors, stroke type, stroke distribution, and involved cerebral vessels were evaluated and compared. Results: The diabetes mellitus incidence in stroke patients with OSAHS was significantly higher than in those without OSAHS. Patients with OSAHS were associated with greater incidence of lobar hemorrhage [OR (95% CI): 5.339 (1.399-20.367); P=0.014] and small-vessel disease [OR (95% CI): 1.797 (1.039-3.107); P=0.036]. Both anterior and posterior cerebral vascular circulations [OR (95% CI): 3.432 (1.920-6.135); P=0.0001] were also affected. Diabetes mellitus and OSAHS were not observed to be correlated for the outcome. Conclusions: Stroke patients with OSAHS are associated with hemorrhage distribution and cerebral infarction etiology, but not with specific patterns of stroke type and topography of cerebral infarction. No interaction was observed between OSAHS and diabetes mellitus.

Keywords: Stroke, obstructive sleep apnea-hypopnea syndrome, diabetes mellitus, interaction

Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common sleep disorder that causes a series of pathophysiological changes in the body. Epidemiological data have indicated that ~9% of middle-aged men and 4% of middle-aged women have OSAHS, and this prevalence is greater in older people [1]. Recent studies have suggested that OSAHS causes 58% increase in the incidence of cerebral infarction and promotes cerebrovascular disease [2]. Yaggi performed a large-scale cohort study of 1,022 patients for nearly 7 years and reported that OSAHS and stroke were significantly correlated (P=0.04). The risk ratio for these events was statistically significant (OR: 1.97, CI: 1.12-3.46; P=0.01) [3]. OSAHS is a definite risk factor for stroke, and the relationship between stroke and OSAHS has been explored with consideration to some common independent risk factors, such as diabetes mellitus and hypertension. However, the potential modification of OSAHS effect caused by diabetes mellitus, which increases the risk of stroke, has not been evaluated yet. Thus, we analyzed the differences between stroke patients with and without OSAHS from multiple medical centers and assessed stroke clinical characteristics, type, topography, and etiology patterns of patients by examining the possible correlation of OSAHS with diabetes mellitus. We investigated the role of OSAHS in stroke and provided further predictive value for stroke.

Methods

Patients

This study was approved by the Binzhou Medical University School of Medicine Institutional Review Board. A retrospective review of the collected database was performed. We analyzed acute stroke patients who were admitted to three medical centers in Shandong Province, China, from January 2013 to June 2014. The

inclusion criteria included the following: (1) patients hospitalized in the first week after stroke onset; (2) patients who meet the diagnostic criteria for stroke by WHO, and images obtained by magnetic resonance imaging (MRI) and diffusion weighted imaging (DWI) can explain the clinical symptoms of lesions; (3) patients can participate in the OSA screening and neuropsychological assessment; and (4) patients can provide complete research-related information (including head and neck MRA).

In the first week of hospitalization, patients were interviewed with a designed questionnaire to determine the presence of common OSA symptoms and monitored some objective indices (thoracic-abdominal movement, SaO_2, and airflow) preliminarily. Subsequently, an overnight polysomnography was performed with the use of the Alice system (Respironics, Murrysville, PA) when needed. Sleep staging was determined by a standard four-channel electroencephalogram (C4A1, C3A2, O4A1, and O3A2), two electroencephalographic leads for arousals (F4A1 and F3M2), two-channel electrooculogram, and submental electromyogram when needed. Continuous measurements of airflow by thermistor and nasal/oral pressure transducer, ribcage and abdominal motion by impedance plethysmography, oxygen saturation by finger oximetry, and movement by leg electromyogram were recorded and analyzed in a standardized fashion. ECG recorded heart rate and rhythm. Sleep stages were scored with the use of standard Rechstchaffen and Kales criteria as modified by American Academy of Sleep Medicine 2007 criteria [4]. OSAHS was defined as the cessation of airflow for >10 s with persistent respiratory effort as seen in the ribcage or abdomen signals; hypopnea was defined as the decrease in airflow and ribcage or abdominal motion by >50% of the baseline signal for >10 s with a ≥4% fall in O_2 saturation. The AHI ≥5 per hour of scored sleep.

The selected patients were grouped into stroke with OSAHS (OSAHS group) and a simple stroke group without sleep apnea syndrome (non-OSAHS group). Clinical baseline characteristics were compared between both groups, including gender, age, BMI [weight/height^2 (kg/m^2)], past medical history (history of hypertension, diabetes mellitus, hyperlipidemia and previous stroke), and history of smoking and alcohol drinking.

Cerebral infarction distribution

Infarct topography was observed by MRI, DWI, and magnetic resonance angiogram (MRA). According to a head and neck MRA, MRI, and DWI, patients were grouped into the anterior circulation infarction group, the posterior circulation infarction group, and both anterior and posterior circulation-involved infarction group. According to brain MRI and DWI, patients were divided by the following anatomic sites: (1) cortical infarction: the anterior cerebral artery in the brain or cortical branch distribution, expressed as the backbone of the middle cerebral artery occlusion, or the brain cortical branch artery occlusion, the anterior cerebral artery, posterior border zone (watershed) infarction, or cerebral artery distribution infarction; (2) basal ganglion infarction: anterior circulation arteriae perforantes distribution; (3) centrum oval infarction: the middle cerebral artery cortical branch and arteriae perforantes distribution of the junction area, mainly located within the border zone corona radiata area; and (4) posterior circulation infarction: vertebrobasilar distribution, including the brainstem, thalamus, and occipital cortex [5, 6].

Etiology of cerebral infarction

Patients were divided into five groups according to the application of TOAST classification (vascular etiologies) as follows: (1) large-artery disease (LAD), (2) cardioembolism (CE), (3) small-vessel disease (SVD), (4) stroke of other determined etiology (SOD), and (5) stroke of undetermined etiology (SUD) [6].

Statistics

Data were analyzed by SPSS 17.0. Age and BMI differences between the groups were analyzed using the student t tests, and all dichotomous variables were assessed using the χ^2 test. After univariate analysis, multivariate logistic regression model analysis was performed to evaluate the potential effect of age, hypertension, BMI, diabetes mellitus and OSAHS on the type of stroke. The influence on the topography and etiology of stroke was evaluated in a similar model. The significance of possible effect modification was tested with interaction terms, which were added to the multivariate model containing individual factors. Statistical analyses were assessed by OR with 95% CI. The statistical significance was $P<0.05$.

Table 1. Clinical characteristics of OSAHS vs. non-OSAHS patients

	Total (n=483)	Non-OSAHS (n=250)	OSAHS (n=233)	T or chi-square value	*P* value
Age, mean SD	64±8.6	63±8.3	67±9.1	5.052	0.000*
Male sex, n (%)	250 (51.8)	121 (48.4)	129 (55.4)	2.343	0.126
Risk factors, n (%)					
Hypertension	182 (37.7)	111 (44.5)	163 (70.0)	32.090	0.000*
Hypercholesterolemia	263 (54.5)	129 (51.6)	134 (57.5)	1.699	0.192
Diabetes mellitus	284 (58.8)	118 (47.2)	166 (71.2)	28.781	0.000*
Homocysteine	311 (64.4)	151 (60.4)	160 (68.7)	3.597	0.058
BMI	27.3±3.0	27.0±2.7	27.9±3.7	3.068	0.002*
Smoking, n (%)	211 (43.7)	100 (40)	111 (47.6)	2.861	0.091
Prior stroke, n (%)	106 (21.9)	52 (20.8)	54 (23.2)	0.397	0.528
AHI		3.8±1.9	26.1±6.2	54.208	0.000*
MAI		3.4±2.7	14.5±5.9	26.881	0.000*
REM (%)		19.9±7.2	12.9±5.3	12.097	0.000*

Data are presented as mean ± SD or number. Abbreviations: BMI, body mass index; OSAHS, obstructive sleep apnea–hypopnea syndrome; AHI, apnea hypopnea index; MAI, microarousal index; REM, rapid eye movement. *P<0.05, statistically significant.

Table 2. Type and topography of strokes in OSAHS vs. non-OSAHS patients

Stroke type	non-OSAHS n=250	OSAHS n=233	Total n=483	T or chi-square value	*P* value
Hemorrhagic, n (%)	50 (20)	37 (15.9)	87 (18)	1.386	0.239
Basal ganglion, n (%)	34 (68)	18 (48.7)	69 (59.8)		
Lobar, n (%)	5 (10)	10 (27.0)	15 (17.2)	4.321	0.038*
Stem-cere**	9 (18)	8 (21.6)	17 (19.5)		
Other, n (%)	2 (4)	1 (2.7)	3 (3.5)		
Ischemic, n (%)	200 (80)	196 (84.1)	396 (82)		
Cortical, n (%)	48 (24)	40 (20.4)	88 (22.2)		
Basal ganglion, n (%)	59 (29.5)	51 (26.0)	110 (27.8)	0.597	0.439
Centrum ovale, n (%)	60 (30)	75 (38.3)	135 (34.1)		
Posterior, n (%)	33 (16.5)	30 (15.3)	63 (15.9)		

Abbreviations: OSAHS, obstructive sleep apnea-hypopnea syndrome. **Hemorrhage in the brainstem or in the cerebellum. *P<0.05, statistically significant.

Results

A total of 483 patients were included in the analysis in which 233 cases were eventually diagnosed with OSAHS, and 250 cases without breathing-related sleep disorder were defined as non-OSAHS (control). The majority of the excluded patients had central sleep apnea. The remaining patients were excluded for other reasons, such as the presence of chronic obstructive or restrictive lung disease. Baseline demographics of the included cohort did not vary significantly from the entire cohort.

The clinical characteristics of the patients with OSAHS and non-OSAHS are depicted in **Table 1**. The mean age of these patients was 64±8.6 years old; 51.8% of the patients were men. A total of 106 patients (21.9%) had clinical history of symptomatic stroke; 284 (58.8%) had diabetes mellitus; 263 (54.5%) had dyslipidemia; and 182 (37.7%) had hypertension. The univariate analysis of all variables between the two groups revealed that the following factors were different between the two groups: diabetes mellitus (47.2% vs. 71.2%; P<0.001), hypertension (44.5% vs. 70.0%; P<0.001), BMI (27.0±2.7 vs. 27.9±3.7; P<0.05), and age (67±9.1 vs. 63±8.3 years old; P<0.001).

Table 2 depicts the cerebral events in our cohort. A total of 396 (82%) patients had infarc-

Table 3. Variable associated with hemorrhage and subgroup analysis according to diabetes mellitus (multiple logistic regression analysis)

Variable	Intracerebral hemorrhage all cases** n=87		Lobar intracerebral hemorrhage*** n=15	
	OR (95% CI, β)	p	OR (95% CI, β)	p
OSAHS	1.118 (0.424-2.948, 0.112)	0.821	5.339 (1.399-20.376, 1.675)	0.014*
DM	3.467 (1.521-7.905, 1.243)	0.003*	0.235 (0.063-0.871, -0.235)	0.030*
OSAHS×DM	0.378 (0.108-1.318, -0.972)	0.127	1.515 (0.091-25.204, 0.415)	0.772

Abbreviations: OSAHS, obstructive sleep apnea-hypopnea syndrome; OR, odds ratio; DM, diabetes mellitus. ***Values adjusted for age, hypertension and BMI. All associations hold, given that the patients had had intracerebral hemorrhage. **Values adjusted for age, hypertension and BMI. All associations hold, given that the patients had had a stroke. *P<0.05, statistically significant.

Table 4. Variable associated with basal ganglion infarction and ante-posterior circulation and subgroup analysis according to diabetes mellitus (multiple logistic regression analysis**)

Variable	Basal ganglion infarction		An-posterior circulation***	
	OR (95% CI, β)	p	OR (95% CI, β)	p
OSAHS	1.125 (0.513-2.466, 0.118)	0.769	3.432 (1.920-6.135, 1.233)	0.0001*
DM	2.192 (1.142-4.209, 0.785)	0.018*	1.085 (0.606-1.944, 0.081)	0.784
OSAHS×DM	1.329 (0.521-3.389, 0.284)	0.551	1.299 (0.627-2.690, 0.261)	0.484

Abbreviations: OSAHS, obstructive sleep apnea-hypopnea syndrome; OR, odds ratio; DM, diabetes mellitus. ***Infarcts in the anterior and posterior circulation. **Values adjusted for age, hypertension and BMI. All associations hold, given that the patients had had ischemic stroke. *P<0.05, statistically significant.

tion stroke, whereas 87 patients (18%) had hemorrhagic stroke. However, the stoke types were not significantly different (P=0.239). After the univariate testing, the OSAHS individuals had higher relative prevalence of lobar hemorrhage (27% vs. 10%, p=0.038). After the multivariate analysis, lobar hemorrhage was positively associated with OSAHS (OR=5.339 [1.399-20.376]; P=0.014) but negatively associated with diabetes mellitus (OR=0.235 [0.063-0.871]; P=0.030). No interaction was observed between the former and the latter, as evidenced by the OR for the stratification of OSAHS patients by diabetes mellitus (**Table 3**).

Among the 396 cases of cerebral infarction, basal ganglia infarction was more common in the OSAHS group but was not statistically different from the controls (26.0% vs. 29.5%, P=0.090). Based on intracranial vascular involvement distinction, both the anterior and posterior circulation infarctions were more common in persons with OSAHS (27.5% vs. 9.5%, P<0.001). After multivariate analysis, OSAHS was associated with greater incidence of anterior and posterior cerebral vascular circulation infarction [OR=3.432 (1.920-6.135); P=0.0001]. No interaction between OSAHS and diabetes mellitus was observed, as evidenced by the estimates of OR for the subgroups of OSAHS diabetic and OSAHS nondiabetic individuals (**Table 4**).

SVD was more common in the OSAHS group (**Table 5**); the association was still significant after multivariate testing. SVD may be associated with OSAHS [OR=1.797 (1.039-3.107); P=0.036] and more strongly associated with diabetes mellitus [OR=2.174 (1.236-3.822); P=0.007]. LAD was positively related to diabetes mellitus but negatively related to OSAHS; no interaction was observed (**Table 6**).

Discussion

Among all the patients who experienced ischemic stroke, 77% of men and 64% of women with stroke suffered from OSAHS [7]. Arzt reported (Wisconsin Sleep Cohort Study) that the incidence of stroke in moderate and severe OSAHS patients was 4.33 times than that of the general population, and OSAHS was an independent risk factor of stroke [8]. Among the stroke patients we followed, 357 cases (50.5%) of stroke patients were diagnosed with SAS. A total of 124 patients that suffered from

Table 5. Etiology of ischemic stroke in OSAHS vs. non-OSAHS patients

Etiology	non-OSAHS	OSAHS	Chi-square value	p	Total (n=396)
Small-vessel disease	25 (12.5)	41 (20.9)	5.900	0.015*	66 (16.7)
Large-artery disease	76 (38.0)	89 (45.4)	3.260	0.071	165 (41.7)
Cardiogenic embolism	31 (15.5)	33 (16.8)			64 (16.2)
Other	12 (6.0)	9 (4.6)			21 (5.3)
Undetermined	56 (28.0)	24 (12.3)			80 (20.1)

Abbreviations: OSAHS, obstructive sleep apnea-hypopnea syndrome. *P<0.05, statistically significant.

Table 6. Variable associated with LAD and SVD and subgroup analysis according to diabetes mellitus (multiple logistic regression analysis**)

Variable	Small-vessel disease		Large-artery disease	
	OR (95% CI, β)	p	OR (95% CI, β)	p
OSAHS	1.797 (1.039-3.107, 0.586)	0.036*	0.713 (0.323-1.797, -0.338)	0.713
DM	2.174 (1.236-3.822, 0.777)	0.007*	2.711 (1.458-5.041, 0.997)	0.002*
OSAHS×DM	1.598 (0.510-5.010, 0.469)	0.421	1.740 (0.649-4.610, 0.554)	0.271

Abbreviations: OSAHS, obstructive sleep apnea-hypopnea syndrome; OR, odds ratio; DM, diabetes mellitus. **Values adjusted for age, hypertension and BMI. All associations hold, given that the patients had had ischemic stroke. *P<0.05, statistically significant.

central or mixed sleep apnea were excluded, whereas 233 of the 357 SAS cases had OSAHS (65.1%). This finding indicates that more than 50% of stroke patients are at risk of being misdiagnosed with non-OSAHA if polysomnography is not routinely used. Cerebrovascular disease does not increase the incidence of central sleep apnea, and stroke patients would be at high risk of OSAHS [9, 10].

Diabetes mellitus is the major risk factor for a spectrum of ischemic and hemorrhagic cerebrovascular diseases. Similarly, studies have shown that OSAHS can arouse apoptosis of islet B cells and induce insulin resistance. The probability of diabetes mellitus increases in OSAHS patients. Approximately 40% of OSAHS patients have diabetes mellitus [11, 12]. Moreover, OSAHS is a common complication in diabetes mellitus patients [11]. In our cohort, diabetes mellitus was observed more frequently in stroke patients with OSAHS, which is consistent with the previous report. Other than diabetes mellitus, OSAHS patients have high cerebrovascular risk factors, such as hypertension, age, and BMI. The incidence of OSAHS in stroke patients would increase with age. The OSAHS group was, on average, 4 years older than the non-OSAHS. This trend was not related to gender. By contrast, other cerebrovascular disease risk factors, such as blood homocysteine, hypercholesterolemia, and smoking in the OSAHS group with stroke, tended to increase without significant difference.

Few reports have depicted the relationship between stroke type and OSAHS. Hence, the understanding remains unclear. In the present study, we observed that OSAHS was more common in ischemic stroke without significant difference (49.49% vs. 42.53%, P>0.05) compared with hemorrhagic stroke. Through logistic multivariate analysis of our cases, we found that OSAHS was still not a factor closely associated with stroke type. This finding was not consistent with Szucs' [13] report, which showed that the incidence and severity of OSAHS in the acute hemorrhagic stroke is significantly higher than in the ischemic group. One probable cause for this variation is the difference in prevalence among different races and geographical origin. Moreover, OSAHS is closely related to some risk factors of stroke. Thus, a more complicated potential impact of these risk factors may lead to the conflicting results. Nevertheless, a prospective cohort study would be helpful for our observation in the future.

As for the bleeding site, deep basal ganglia hemorrhage accounted for the largest proportion of cerebral hemorrhage patients with OSAHS, but the difference did not reach the significance level. However, lobar hemorrhages were more frequent in the OSAHS group com-

pared with the non-OSAHS group. The difference between the two groups was statistically significant. OSAHS was closely associated with lobar hemorrhage, whereas diabetes mellitus with lobar hemorrhage was not significantly correlated. No statistically significant correlation between OSAHS and diabetes mellitus for lobar hemorrhage was observed. Lobar hemorrhage occurred in the frontal lobe in the OSAHS group, with the following priority order: frontal > parietal > temporal > occipital lobe. We speculated that airway obstruction in OSAHS patients may affect the frontal gyrus, which controls pharyngeal muscle contraction to avoid active airway narrowing, and the overactivity and lower relative tolerance to hypoxic exposure and abnormal regulation of vascular endothelial function eventually results in bleeding. In view of the relativity between cognitive impairment and frontal lobe stroke, this finding may strengthen the arguments that OSAHS led to cognitive decline in patients with stroke.

Bassetti [14] reported that OSAHS is related to the site and severity of cerebral infarction. However, Parra and others [15] showed conflicting results. The clinical relevance of OSAHS with cerebral infarction distribution and vascular involvement is controversial. The incidence of both anterior and posterior vascular circulation involvement was significantly higher in the OSAHS group. In addition, the anterior and posterior vascular circulations, which are extensively involved, was closely related to OSAHS but not strongly associated with diabetes mellitus. The subgroup analysis showed the absence of interaction. In our cohort, patients with OSAHS had relatively higher prevalence of deep basal ganglia infarction but were not statistically significant. OSAHS distributions showed no significant difference among patients having different locations of cerebral infarction. However, studies have confirmed a close relationship between OSAHS and white matter lesions [16, 17] in which basal ganglia infarction was considered a risk factor. Therefore, prospective cohort studies are needed to explore the existence of reciprocal causation.

Several recent studies have shown that OSAHS significantly increased the incidence of white matter lesions [16, 17]. An SWI study in China found that OSAHS could be a risk factor for cerebral microbleeds. It is suggested that OSAHS is intimately connected to cerebral small vessel disease (SVD). Based on this finding, whether SVD is more common in the OSAHS group, needs to be further investigated. Currently, only few reports have explained the relationships between OSAHS and stroke vascular etiologies. In our cohort, we found that the incidence of SVD in the OSAHS group was significantly higher. Diabetes mellitus was more closely linked with SVD, and diabetes mellitus was not found to interact with OSAHS. It has been demonstrated that airway obstruction, hypoxia during sleep, autonomic nervous system dysfunction occurs in OSAHS patients destroys the physiological circadian rhythm of blood pressure, causing hypertensive arteriosclerosis [18-20]. Lavie L confirmed that oxidative stress in OSAHS patients could induce activation damage of vascular endothelial cell, and increase vascular permeability [21, 22]. Additionally, in OSAHS patients, cerebral autoregulation is impaired, which lead to decreased cerebral perfusion [23]. The underlying association of OSAHS with SVD may be explained by these findings.

This study was limited by a small sample size and selection bias, and the OSAHS group was not a complete representative of the characteristics of stroke patients.

Further studies are needed to determine the complicated interaction between OSAHS and risk factors. In addition, more prospective studies are required to seek the cause and effect relationship in determining whether OSAHS treatment after stroke is important in stroke prevention.

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Disclosure of conflict of interest

None.

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References

[1] Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. Prog Cardiovasc Dis 2009; 51: 285-293.

[2] Floras JS. Hypertension, sleep apnea, and atherosclerosis. Hypertension 2009; 53: 1-3.

[3] Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM and Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005; 353: 2034-2041.

[4] Iber C, Ancoli-Israel S, Chesson A, Quan SF; For the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st edition. Westchester (IL): American Academy of Sleep Medicine; 2007.

[5] In: Ginsberg MD, Bogousslavsky J, editors. Cerebrovascular disease: pathophysiology, diagnosis, and management. Malden: Blackwell Sci; 1998. pp. 921-930

[6] Karapanayiotides T, Piechowski-Jozwiak B, van Melle G, Bogousslavsky J and Devuyst G. Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. Neurology 2004; 62: 1558-1562.

[7] Dyken ME, Somers VK, Yamada T, Ren ZY and Zimmerman MB. Investigating the relationship between stroke and obstructive sleep apnea. Stroke 1996; 27: 401-407.

[8] Arzt M, Young T, Finn L, Skatrud JB and Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med 2005; 172: 1447-1451.

[9] Parra O, Arboix A, Montserrat JM, Quinto L, Bechich S and Garcia-Eroles L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. Eur Respir J 2004; 24: 267-272.

[10] Johnson KG and Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. J Clin Sleep Med 2010; 6: 131-137.

[11] Shaw JE, Punjabi NM, Wilding JP, Alberti KG, Zimmet PZ; International Diabetes Federation Taskforce on Epidemiology and Prevention. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. Diabetes Res Clin Pract 2008; 81: 2-12.

[12] Resnick HE, Redline S, Shahar E, Gilpin A, Newman A, Walter R, Ewy GA, Howard BV, Punjabi NM; Sleep Heart Health Study. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. Diabetes Care 2003; 26: 702-709.

[13] Szucs A, Vitrai J, Janszky J, Migleczi G, Bodizs R, Halasz P and Nagy Z. Pathological sleep apnoea frequency remains permanent in ischemic stroke and it is transient in hemorrhagic stroke. Eur Neurol 2002; 47: 15-19.

[14] Bassetti C, Aldrich MS and Quint D. Sleep-disordered breathing in patients with acute supra- and infratentorial strokes. A prospective study of 39 patients. Stroke 1997; 28: 1765-1772.

[15] Parra O, Arboix A, Bechich S, Garcia-Eroles L, Montserrat JM, Lopez JA, Ballester E, Guerra JM and Sopena JJ. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. Am J Respir Crit Care Med 2000; 161: 375-380.

[16] Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, O'Connor GT, Boland LL, Schwartz JE and Samet JM. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001; 163: 19-25.

[17] Kamba M, Inoue Y, Higami S, Suto Y, Ogawa T and Chen W. Cerebral metabolic impairment in patients with obstructive sleep apnoea: an independent association of obstructive sleep apnoea with white matter change. J Neurol Neurosurg Psychiatry 2001; 71: 334-339

[18] Peppard PE, Young T, Palta M and Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. New Engl J Med 2000; 342: 1378-1384

[19] Ziegler MG, Mills PJ, Loredo JS, Ancoli-Israel S and Dimsdale JE. Effect of continuous positive airway pressure and placebo treatment on sympathetic nervous activity in patients with obstructive sleep apnea. Chest 2001; 120: 887-893.

[20] Sharabi Y, Dagan Y and Grossman E. Sleep apnea as a risk factor for hypertension. Curr Opin Nephrol Hypertens 2004; 13: 359-364.

[21] Lavie L. Obstructive sleep apnoea syndrome--an oxidative stress disorder. Sleep Med Rev 2003; 7: 35-51.

[22] Lavie L, Vishnevsky A and Lavie P. Evidence for lipid peroxidation in obstructive sleep apnea. Sleep 2004; 27: 123-128.

[23] Tsivgoulis G and Alexandrov AV. Cerebral autoregulation impairment during wakefulness in obstructive sleep apnea syndrome is a potential mechanism increasing stroke risk. Eur J neurol 2009; 16: 283-284.