Neuropathy and Dysautonomia in Patients with Obstructive Sleep Apnea Syndrome

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ABSTRACT

Introduction: The aim of our study is to search for the existence of neuropathy, dysautonomia and to identify the correlations of sickness level of patients with Obstructive Sleep Apnea Syndrome (OSAS).

Methods: The research is based on the real cases at Dokuz Eylül University of Medicine Sleep and Epilepsy Center; observed during September 2008-May 2009. The patients were selected by polysomnography samples based on 20 persons at same ages with following criteria; high leveled OSAS (AHİ≥30), low OSAS (5≤AHİ<30) and healthy participants. Classical ENMG protocol, sympathetic skin response and R-R interval variation test were performed on these samples.

Results: High and low leveled OSAS patients had a statistically significant ($p<0.05$) decrease in the average velocity of motor conduction in right tibialis posterior when compared to the control group. Besides we observed an statistically significant ($p<0.05$) increase in the average amplitude of sympathetic skin responses in high leveled OSAS patients than control group.

Conclusion: OSAS indicates a risk of possible peripheral neuropathy and autonomic dysfunction risk increases in positive correlation with level of OSAS.

Keywords: OSAS, neuropathy, autonomic dysfunction

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive upper airway occlusions during sleep that affects 1–4% of adult men and 1–2% of adult women (1,2). The most common night symptom is snoring and daytime symptom is somnolence (3). OSAS causes serious morbidity and mortality as a result of its cardiovascular complications (4,5,6,7). The main cause of morbidity and mortality is secondary to recurrent hypoxia pathologies. Arterial hypertension, atherosclerosis, cardiac arrhythmia, coronary artery disease, ischemic stroke, peripheral axonal neuropathy, and diabetes mellitus are known to be associated with OSAS (8,9,10,11,12).

There is no classical evidence about repetitive hypoxia in chronic obstructive sleep apnea affecting the peripheral nervous system (13). The results of recent studies showed that the repetitive hypoxia in OSAS is a reason of polyneuropathy (10,11,12). Repetitive hypoxia induces the dysfunction of the autonomic nervous system by activating the sympathetic system through chemoreceptor reflexes (14). Autonomic dysfunction can be evaluated with noninvasive methods such as called sympathetic skin response (SSR) and RR interval variability (RRIV). In the literature, there are few studies assessing autonomic dysfunction in OSAS patients using these methods. Zakrzewska et al. (15) found that SSR latencies prolonged in OSAS patients compared with the control group and no significant difference was detected in RRIV latencies. Pierzchała et al. (16) showed a decrease in the amplitude of SSR in OSAS patients compared with the control group.

The aim of this study was to investigate the presence of autonomic dysfunction and peripheral neuropathy in OSAS patients and to clarify the relationship between the stage of the disease and these conditions.

METHODS

The study was started after confirmation from Dokuz Eylül University Faculty of Medicine Ethics Committee. Patients with snoring and excessive daytime sleepiness were included in study between September 2008 and May 2009 from Dokuz Eylül University

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Faculty of Medicine Sleep Center. Seventy-two patients were prospectively included in the study after obtaining each patient's informed consent, according to American Academy of Sleep Medicine (17) criteria for the diagnosis of OSAS. All cases had no continuous positive airway pressure therapy. Thirty-two patients were out of the study because of collagen tissue disease, cardiac arrhythmia, amyloidosis, chronic renal failure, malignancy, diabetes mellitus, and a disease or drug that could affect the autonomic nervous system (15). Forty OSAS patients were divided into two groups according to the values of the apnea-hypopnea index (AHI). The first group was severe OSAS ($AHI \geq 30$) and the second group was mild OSAS ($5 \leq AHI < 30$). Also 20 healthy subjects were included as a control group whose Epworth sleepiness scores (18) were "0." Patients were interrogated prior to the tests to determine whether which factors can affect the autonomic system, such as anticholinergic medication, caffeine, tobacco, and vasodilator drugs. Patients were tested using the classical electrophysiological polyneuropathy protocol, SSR, and RRIV, and the results were compared between the three groups (19,20).

Polysomnography

Recording of patients was initiated from 22:00 to 24:00 and was terminated the next day at 07:00. Embla A10 (Embla, Colorado, USA) polysomnographic device was used and scored manually according to the criteria of Rechtschaffen and Kales (21). It was recorded during the night, mean and minimal arterial oxygen saturation was measured by finger oximetry, AHI, arterial oxygen saturation range below 90%.

ENMG

Polyneuropathy Protocol

It was used to measure amplitude and conduction velocities using the Medtronic/Keypoint brand device. In this method, antidromic submaximal stimulus is given to the left ulnar sensory and motor nerves, the left peroneal motor nerve, the right motor posterior tibial nerve, and the sural sensory nerve (19).

Sympathetic Skin Response

The Medtronic/Keypoint brand ENMG device autonomic nervous system test program was used for SSR. Test was performed in a quiet and dimly-lit room to avoid external stimulus. The skin temperature was kept around near 32°C and silver chloride disc electrodes were used. The active electrodes were placed on the palm of the hand and on the medial portion of the foot. The reference electrodes were placed on the back of the hand and on the dorsal surface of the foot. Ground electrodes were attached to the wrist and ankle. A recorder system calibrated the lower frequency limit 0.1–2.0 Hz and the upper frequency limit from 100 to 2000 Hz. Rectangular single electric shocks were given at a 0.2–0.5-ms duration and 0–30 mA to each extremity bilaterally. It was necessary to wait at least 60 s to prevent habituation. Latency and amplitude were examined by the evaluation of the first positive or negative deflection. The "peak to peak" distance was used to calculate the amplitude (20).

RR Interval Variability

The Medtronic/Keypoint brand ENMG device autonomic nervous system test program was used for the RRIV. ECG electrodes were placed at two precordial foci ($V_1 - V_4$). RRIV was evaluated at rest, while deep breathing, from a sitting position to standing up, and at Valsalva maneuver (20).

Statistical Analysis

Data were evaluated by Statistical Package for the Social Sciences (SPSS) 15.0. For the comparison between the three groups' parameters, the Kruskal-Wallis variance analysis was used. For the verification of the parameters that detected significant differences, Bonferroni correction test was used and a p-value of <0.05 was considered statistically significant.

RESULTS

The control group contained one female and 19 male participants; the mean age was 51 years (range 33–73 years) and mean body mass index (BMI) was 29.6 kg/m² (range 23.7–43.1 kg/m²). The mild OSAS group included three female and 17 male participants; the mean age was 46.5 years (range 26–71 years), mean BMI was 27.4 kg/m² (range 23.7–43.1 kg/m²), and mean AHI was 18.2 (range 6.9–29.7). The severe OSAS group contained 20 male participants; the mean age was 48 years (range 30–65 years), mean BMI was 29.9 kg/m² (range 24.1–38.3 kg/m²), and mean AHI was 55 (range 31.8–60.3). No statistically significant difference between was observed in both groups in terms of age and BMI ($p>0.05$) (Table 1).

In the study, left ulnar sensory and motor, left peroneal motor, right posterior tibial motor, and right sural sensory nerves were examined. Only the right posterior tibial motor nerve conduction velocity decreased, and it was statistically significant in the OSAS group compared with the control group. The mean posterior tibial motor nerve conduction velocity in the control group was 48.7 m/s (range 43.5–57.8 m/s), in the mild OSAS group was 45.6 m/s (range 38.5–60.3 m/s), and in the severe OSAS group was 45.7 m/s (range 40.3–61.6 m/s). The right posterior tibial motor nerve conduction velocities of the mild and severe OSAS groups were significantly decreased ($p=0.03$) compared with the healthy control group, whereas there was no statistically significant difference between the mild and severe OSAS groups ($p=0.42$) (Table 2). There was no correlation between the tibialis posterior nerve conduction velocity and minimal oxygen saturation ($p=0.30$).

There was no statistically significant difference between the groups in the mean SSR latency ($p>0.05$). There was a statistically significant difference between the control group and the severe OSAS group in the SSR amplitude values at upper ($p=0.043$) and lower extremities ($p=0.024$). There was no statistically significant difference between the mild OSAS group and the other two groups ($p>0.05$) (Tables 3,4).

When RR interval variabilities were examined, there was no statistically significant difference between the groups ($p>0.05$) (Table 5).

Table 1. Comparison of demographic data and apnea-hypopnea index

	Severe OSAS	Mild OSAS	Control	p
Age (year)	48 (30-65)	46.5 (26-71)	51 (33-73)	0.87
Male (n)	20	17	19	
Female (n)	0	3	1	
BMI (kg/m ²)	29.9 (24.1-38.3)	27.4 (20.8-40)	29.6 (23.7-43.1)	0.08
AHI	55 (31.8-60.3)	18.2 (6.9-29.7)		0.00
MOS (%)	75.8 (62-87)	84.9 (73-90)		0.02

OSAS: obstructive sleep apnea syndrome; Values: median (minimum–maximum); AHI: apnea-hypopnea index; BMI: body mass index; MOS: minimal oxygen saturation

Table 2. Comparison of neural conduction parameter between control and OSAS groups

	Severe OSAS	Mild OSAS	Control	p
S.Ulnar.A. (mV)	19.1 (6.5-34.5)	17.8 (12.1-53.5)	16.9 (10.5-25.9)	0.82
S.Ulnar.V. (m/s)	57.4 (34-72.2)	55.6 (42.4-67.5)	54.5 (44.6-62.5)	0.11
S.Sural.A. (mV)	10.9 (5-27)	10.1 (3-19)	10.9 (6-33)	0.71
S.Sural.V. (m/s)	47.8 (43-68)	52.2 (38-64)	50 (43-69)	0.39
M.Ulnar.L. (ms)	2.6 (0.7-3.3)	2.6 (2-3.2)	2.8 (1.5-3.5)	0.56
M.Ulnar.Di.A. (mV)	11.8 (5.2-16.8)	11.3 (6.7-18.5)	12.9 (8.2-24.7)	0.22
M.Ulnar.Pr.A. (mV)	9.3 (3.9-15.5)	11.1 (7.7-15.8)	11.4 (5.5-17)	0.13
M.Ulnar.V. (m/s)	55.2 (44.5-77.7)	61.5 (48.9-69.9)	57.7 (51-70.2)	0.62
Peroneal.L. (ms)	4.3 (3.1-7.7)	4.3 (3.2-5.8)	4.6 (3.3-7.1)	0.56
Peroneal.Di.A.(mV)	3.9 (2.1-9.8)	2.9 (0.3-11)	3.8 (0.9-14.3)	0.77
Peroneal.Pr.A.(mV)	3.8 (1.6-7.1)	4.2 (0.2-11)	3.2 (1.1-14.7)	0.39
Peroneal.V. (m/s)	50.9 (45-61)	51.7 (46-61)	49.7 (44-68.6)	0.75
Tibial.L. (ms)	4 (2.4-6.1)	4.2 (2.5-6.8)	5.07 (2.9-6.7)	0.56
Tibial.Di.A. (mV)	10.4 (3-16)	9.09 (3-26)	10.1 (3-21)	0.65
Tibial.Pr.A. (mV)	7.4 (3.2-11.6)	8.2 (2.9-17.6)	9.05 (2.1-14)	0.09
Tibial.V.* (m/s)	45.7 (40.3-61.6)	45.6 (38.5-60.3)	48.7 (43.5-57.8)	0.03

OSAS: obstructive sleep apnea syndrome; Values: median (minimum–maximum); A: amplitude; L: latency; V: velocity; S: sensory; M: motor; Di: distal; Pr: proximal. *p<0.05

DISCUSSION

OSAS is a clinical situation characterized by recurrent upper airway obstruction during sleep (1,2). It was shown that hypoxia associated with arterial microcirculation causes capillary endothelial cell hyperplasia, increasing the degree of hypoxia. Repetitive hypoxia may cause autonomic dysfunction through chemoreceptor reflex by the activation of the sympathetic system (22,23,24). There are few studies in the literature that showed the relationship between OSAS and autonomic dysfunction (15,16). There is no study that compares polyneuropathy and autonomic dysfunction according to the severity of OSAS. The aim of this study was to investigate the relationship of the severity of OSAS with neuropathy and autonomic dysfunction.

In this study, 20 healthy patients, 20 mild OSAS ($5 \leq \text{AHI} < 30$), and 20 severe OSAS ($\text{AHI} \geq 30$) patients' nerves were examined by ENMG. These nerves were the left ulnar sensory and motor, the left peroneal 26 motor, the right tibialis posterior motor, and the right sural sensory

Table 3. Comparison of sympathetic skin response variables

	Severe OSAS	Mild OSAS	Control	p
Up Latency (ms)	1484 (1224-3263)	1502 (1071-2487)	1521 (1231-1920)	0.79
Up Amplitude (mV)*	1.04 (0.3-4.7)	0.97 (0.3-3.1)	0.78 (0.1-1.5)	0.04
Low Latency (ms)	2149 (1659-3870)	2002 (1617-2794)	1960 (1557-2503)	0.17
Low Amplitude (mV)*	0.83 (0.12-2.1)	0.478 (0.13-1.8)	0.472 (0.06-1.05)	0.02

OSAS: obstructive sleep apnea syndrome; Values: median (minimum–maximum); Up: upper extremity; Low: lower extremity.
*p<0.05

Table 4. Comparison of sympathetic skin response variables

	Up Amplitude	Low Amplitude
Severe OSAS–control (p)	0.043*	0.024*
Severe–mild OSAS (p)	0.52	0.39
Mild OSAS–control (p)	0.21	0.31

OSAS: obstructive sleep apnea syndrome; *p<0.05, Up: upper extremity; Low: lower extremity

nerves. In the OSAS group, the right posterior tibial motor nerve conduction velocity decreased, and it was statistically significant. There was no statistically significant difference between the mild and severe OSAS groups ($p=0.42$) (Table 2). Mayer et al. (10) examined median nerves in 17 OSAS patients ($\text{AHI} > 40$) and 10 healthy patients. Median sensory nerve amplitudes of OSAS patients decreased significantly. Lüdemann et al. (11) examined right peroneal nerve amplitudes and velocities in 23 OSAS patients ($\text{AHI} > 10$) and 21 healthy patients. The left sural nerves amplitude of OSAS patients decreased significantly. Dzięwas et al. (12) examined bilateral sural nerve amplitudes in 23 OSAS patients ($\text{AHI} > 10$) and 23 healthy patients. Bilateral sural nerve amplitudes of OSAS patients decreased significantly. In previous studies, the posterior tibial motor nerves in OSAS patients have not been studied. In this study only, the tibialis posterior motor nerves affected. The previous OSAS and neuropathy study methods and results were heterogeneous; thus, to compare our work and the other methods is very difficult. This study supports previous studies in case of the cause of OSAS in the formation of peripheral neuropathy. There is no correlation between the severity of OSAS, minimal oxygen saturation (MOS), and neuropathy. The number of cases similar to the methodology of the studies to discuss the association between OSAS and neuropathy is warranted to work.

In this study, 20 healthy patients, 20 mild OSAS ($5 \leq \text{AHI} < 30$) patients, and 20 severe OSAS ($\text{AHI} \geq 30$) patients were evaluated with SSR and RRIV. The SSR latency and RRIV among the groups showed no statistically significant difference. SSR amplitudes in the severe OSAS group were significantly increased compared with the control group; however, those between the control group with mild OSAS and mild OSAS with severe OSAS did not significantly differ ($p > 0.05$) (Tables 3,4). Zakrzewska et al. (15) compared autonomic symptoms between 34 OSAS patients ($\text{AHI} > 5$) and 32 healthy patients and found that when the

Table 5. Comparison of RR interval variabilities

	Severe OSAS	Mild OSAS	Control	p
Rest (%)	15 (5.7-52.4)	13.7 (4.2-49.3)	13.1 (7.7-29.8)	0.83
Deep (%)	35.9 (13.8-69.8)	24.55 (14.1-52.9)	28.7 (13.8-50.8)	0.45
Valsalva (max/min)	1.3 (0.12-2.1)	1.2 (1.07-2.4)	1.3 (1.04-1.8)	0.69
Standing (max/min)	1.04 (0.95-1.26)	1.03 (0.2-1.17)	1.06 (0.9-1.17)	0.38

OSAS: obstructive sleep apnea syndrome; Values: median (minimum–maximum); Rest: the maximum–minimum percentage variation variability at rest position; Deep: the maximum–minimum percentage variation variability at deep breathing; Valsalva: maximum/minimum ratio at Valsalva maneuver; Standing: maximum/minimum ratio of getting up from the sitting to stand position

SSR latency extended in the OSAS group compared with the control group, RRIV was not significantly different between the two groups. Pierzchała et al. (16) compared SSRs in 26 untreated severe OSAS patients and 27 control patients and found that no SSR was observed in 10 OSAS patients and SSR amplitudes were decreased in 16 OSAS patients compared with the control group; however, their findings of upper extremities were significant ($p < 0.001$), the lower limbs were insignificant. In our study, no significant difference was observed between SSR latencies and in severe OSAS patients, the amplitude of SSR was increased significantly compared with the control group. The increase in the amplitude of OSAS might be due to the dysfunction of the autonomic sympathetic system connected to overstimulation. While in the severe OSAS group, the SSR amplitude increased, this not observed in the mild OSAS group; therefore, it might be seen autonomic dysfunction by progression of disease. The absence of a statistically significant correlation between MOS and amplitudes of SSR suggested that OSAS causes autonomic dysfunction, except of hypoxia. The autonomic nervous system has critical importance in the stability of heart rate, blood pressure regulation, and cardiovascular system. Suppressed cardiac vagal activity caused ventricular arrhythmias and sudden death; therefore, the early diagnosis of subclinical autonomic dysfunction is important for planning treatment and determining risk analysis (14,25,26,27). Electrophysiological tests are non-invasive and easy to apply. The use of these tests can help in the early diagnosis of autonomic dysfunction in OSAS patients.

Limitations of this study are the asymptomatic patients included in the study and the scarce number of patients. It is possible to achieve more precious results with autonomic dysfunction symptoms in a large series of patients in further studies.

In conclusion, this study supports that increasing severity of OSAS could cause autonomic dysfunction. ENMG is a non-invasive test that can be applied easily to detect autonomic dysfunction. The routine use of this test for autonomic dysfunction is helpful for preventing sudden cardiac death in OSAS patients.

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REFERENCES

- Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. *Annu Rev Med* 1976; 27:465-484. [\[CrossRef\]](#)
- Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. *Thorax* 1991; 46:85-90. [\[CrossRef\]](#)
- Kales A, Cadieux RJ, Bixler EO, Soldatos CR, Vela-Bueno A, Misoul CA, Locke TW. Severe obstructive sleep apnea-I: Onset, clinical course, and characteristics. *J Chronic Dis* 1985; 38:419-425. [\[CrossRef\]](#)
- Bonsignore MR, Marrone O, Insalaco G, Bonsignore G. The cardiovascular effects of obstructive sleep apnoeas: analysis of pathogenic mechanisms. *Eur Respir J* 1994; 7:786-805. [\[CrossRef\]](#)
- Shahani BT, Day TJ, Cros D, Khalil N, Kneebone CS. RR interval variation and the sympathetic skin response in the assessment of autonomic function in peripheral neuropathy. *Arch Neurol* 1990; 47:659-664. [\[CrossRef\]](#)
- Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990; 336:261-264. [\[CrossRef\]](#)
- Leung RS, Bradley TD. Sleep apnea and cardiovascular disease. *Am J Respir Crit Care Med* 2001; 164:2147-2165. [\[CrossRef\]](#)
- Shneerson JM. *Sleep Medicine: A Guide to Sleep and its Disorders* (Second Edition). Wiley-Blackwell, Oxford 2005; 1-22, 229-262.
- Davies RJ. Cardiovascular aspects of obstructive sleep apnoea and their relevance to the assessment of the efficacy of nasal continuous positive airway pressure therapy. *Thorax* 1998; 53:416-418. [\[CrossRef\]](#)
- Mayer P, Dematteis M, Pépin JL, Wuyam B, Veale D, Vila A, Lévy P. Peripheral neuropathy in sleep apnea. A tissue marker of the severity of nocturnal desaturation. *Am J Respir Crit Care Med* 1999; 159:213-219. [\[CrossRef\]](#)
- Lüdemann P, Dziewas R, Sörös P, Happe S, Frese A. Axonal polyneuropathy in obstructive sleep apnoea. *J Neurol Neurosurg Psychiatry* 2001; 70:685-687. [\[CrossRef\]](#)
- Dziewas R, Schilling M, Engel P, Boentert M, Hor H, Okegwo A, Lüdemann P, Ringelstein EB, Young P. Treatment for obstructive sleep apnoea: effect on peripheral nerve function. *J Neurol Neurosurg Psychiatry* 2007; 78:295-297. [\[CrossRef\]](#)
- Appenzeller O, Parks RD, MacGee J. Peripheral neuropathy in chronic disease of the respiratory tract. *Am J Med* 1968; 44:873-880. [\[CrossRef\]](#)
- Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995; 96:1897-1904. [\[CrossRef\]](#)
- Zakrzewska-Pniowska B, Nojszewska M, Przybylowski T, Byśkiniewicz K. Clinical versus electrophysiological assessment of dysautonomia in obstructive sleep apnea syndrome. *J Clin Neurophysiol* 2004; 21:435-439. [\[CrossRef\]](#)
- Pierzchała K, Łabuz-Roszak B, Ograbek M, Tazbirek M. Neurophysiological investigations in patients with sleep apnoea syndrome. *Wiad Lek* 2002; 55:685-690.
- Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; 22:667-689.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* Dec 1991; 14:540-545.
- Reinhardt F, Wetzell T, Vetten S, Radespiel-Tröger M, Hilz MJ, Heuss D, Neundörfer B. Peripheral neuropathy in chronic venous insufficiency. *Muscle Nerv* 2000; 23:883-887. [\[CrossRef\]](#)
- Ertekin C. Santral ve periferik içinde. I. Baskı. EMG: Bornova, Meta Basım 2006: s.195-211, s.883-911.
- Rechtschaffen A, Kales A. A manual of standardized terminology, techniques, and scoring system for sleep stages in human adults. Washington DC; US Government Printing Office 1968.
- Narayan M, Ferranti R. Nerve conduction impairment in patients with respiratory insufficiency and severe chronic hypoxemia. *Arch Phys Med Rehabil* 1978; 59:188-192.

23. Pfeiffer G, Kunze K, Bruch M, Kutzner M, Ladurner G, Malin JP, Tackmann W. Polyneuropathy associated with chronic hypoxaemia: prevalence in patients with chronic obstructive pulmonary disease. *J Neurol* 1990; 237:230-233. [\[CrossRef\]](#)
24. Valli G, Barbieri S, Sergi P, Fayoumi Z, Berardinelli P. Evidence of motor neuron involvement in chronic respiratory insufficiency. *J Neurol Neurosurg Psychiatry* 1984; 47:1117-1121. [\[CrossRef\]](#)
25. Micieli G, Manni R, Tassorelli C, Osipova V, Tartara A, Nappi G. Sleep-apnoea and autonomic dysfunction: a cardiopressor and pupillometric study. *Acta Neurol Scand* 1995; 91:382-388. [\[CrossRef\]](#)
26. Vanninen E, Tuunainen A, Kansanen M, Uusitupa M, Lämsimies E. Cardiac sympathovagal balance during sleep apnea episodes. *Clin Physiol* 1996; 16:209-216. [\[CrossRef\]](#)
27. Veale D, Pepin JL, Levy PA. Autonomic stress tests in obstructive sleep apnea syndrome and snoring. *Sleep* 1992; 15:505-513.