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Peripheral Nerve Function Changes Due to Hypoxia in Obstructive Sleep Apnea

Obstrüktif Uyku Apne'de Hipoksiye Bağlı Periferal Sinir Fonksiyonu Değişiklikleri

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Abstract

Introduction: Chronic hypoxia is known to be one of the risk factors for peripheral neuropathy. However, the effect of intermittent hypoxia on peripheral nerves is not fully understood. This study evaluated the relation between intermittent hypoxia and peripheral nerve function in Obstructive Sleep Apnea (OSA) patients.
Materials and Methods: In this retrospective study, 86 patients who underwent polysomnography (PSG) and electroneuromyography were enrolled. Participants with diseases affecting peripheral nerves and lung function were excluded from the study. Hypoxia parameters were obtained from the PSG study. Lower extremity motor and sensory nerve conduction studies of all patients were evaluated.
Results: In patients with OSA, peroneal nerve distal motor latency and sural sensory nerve action potential amplitude was low and velocity was significantly slower than controls ($p<0.001$, $p<0.04$, $p<0.001$, respectively). After adjustment for age and body mass index, the results remained significantly ($p<0.001$, $p<0.01$, $p<0.001$, respectively). The nerve conduction results were significantly correlated with the hypoxia parameters. After adjustment for confounding factors, logistic regression analyses revealed that hypoxia parameters were independently associated with nerve conduction results.
Conclusion: OSA and intermittent hypoxia may affect both motor and sensory nerve conduction, which suggests that subclinical sensorimotor peripheral neuropathy is associated with OSA. The related intermittent hypoxia and OSA may be a cause of axonal and demyelinating neuropathies.
Keywords: Sleep Apnea syndrome, sleep-disordered breathing, electromyography, hypoxia, neuropathy

Öz

Amaç: Periferik nöropati için risk faktörlerinden birinin kronik hipoksi olduğu bilinmektedir. Bununla birlikte, aralıklı hipoksinin periferal sinirler üzerindeki etkisi tam olarak anlaşılamamıştır. Bu çalışmada Obstrüktif Uyku Apnesi (OSA) hastalarında aralıklı hipoksi ve periferik sinir fonksiyonu arasındaki ilişki değerlendirildi.
Gereç ve Yöntem: Bu retrospektif çalışmaya polisomnografi (PSG) ve elektronöromiyografi uygulanmış 86 hasta alındı. Periferik sinirleri ve akciğer fonksiyonlarını etkileyen hastalıkları olan katılımcılar çalışma dışı bırakıldı. Hipoksi parametreleri PSG çalışmasından elde edildi. Tüm hastaların alt ekstremite motor ve duyu siniri iletim çalışmaları değerlendirildi.
Bulgular: OSA'lı hastalarda kontrollere göre peroneal sinir distal motor latansı ve sural duyusal sinir aksiyon potansiyeli amplitüdü düşük ve hızı anlamlı olarak yavaştı ($p<0,001$, $p<0,04$, $p<0,001$, sırasıyla). Yaş ve vücut kitle indeksi için ayarlama yapıldıktan sonra, sonuçlar anlamlı kaldı ($p<0,001$, $p<0,01$, $p<0,001$, sırasıyla). Sinir iletim sonuçları hipoksi parametreleri ile anlamlı olarak korele idi. Karıştırıcı faktörler ayarlandıktan sonra, lojistik regresyon analizleri, hipoksi parametrelerinin sinir iletimi sonuçlarıyla bağımsız olarak ilişkili olduğunu gösterdi.
Sonuç: OSA ve aralıklı hipoksi, hem motor hem de duyusal sinir iletimini etkileyebilmekte, bu da subklinik sensorimotor periferik nöropatinin OSA ile ilişkili olduğunu düşündürmektedir. OSA ve ilgili aralıklı hipoksi, aksonal ve demiyelinizan nöropatinin bir nedeni olabilir.
Anahtar Kelimeler: Uyku Apne sendromu, uykuda solunum bozukluğu, elektromiyografi, hipoksi, nöropati

Introduction

Obstructive Sleep Apnea (OSA) is common in the general population. Recurrent episodes of the collabing upper airway during sleep, and the resulting intermittent hypoxia, are important features of OSA. The reported estimated prevalence of OSA in adults is 3~7% for males and 2~5% for females (1). During OSA, intermittent cycles of falling oxygen saturation and reoxygenation, and rises in pharyngeal resistance and esophageal pressure, microarousal, and hypercapnia occur.

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The chronic cycles of desaturation-reoxygenation during intermittent hypoxia induce oxidative stress, producing an inflammatory response and reactive oxygen species, which are responsible for OSA-related complications, such as metabolic, neurocognitive, and cardiovascular disorders (2,3).

In patients with chronic obstructive pulmonary disease (COPD) neurophysiological changes have been found in in 90% of the cases. The reported high incidence is thought to be related to hypoxia (4,5). Chronic hypoxia induces peripheral polyneuropathy and this form of nerve damage is associated with the severity and duration of hypoxia (6-8). Prevalence of polyneuropathy due to chronic hypoxia have been reported in a similar range of 28% to 70% in patients with OSA and COPD (5,9-11).

Previous studies have reported that peripheral nerve sensory amplitudes are impaired in OSA patients, but the relationship with hypoxemia has not been fully elucidated (9,12,13). We hypothesized that patients with severe OSA and hypoxia show significantly impaired peripheral nerve conduction compared to controls. In this study, patients were subgrouped according to hypoxia parameters and the apnea-hypopnea index (AHI). Following this we determined whether the severities of OSA and hypoxia were associated with lower extremity motor and sensory nerve conduction abnormalities.

Materials and Methods

Patient's Characteristics

This retrospective study was performed at the neurology outpatient clinic of university hospital. Subjects who underwent polysomnography (PSG) at our sleep disturbance center (accredited by the Turkish Sleep Association) and who underwent nerve conduction studies (NCSs) between October 2008 and January 2018 were selected. In the patients' medical histories, the presence of vascular risk factors and systemic diseases were recorded. Exclusion criteria were patients aged under 18 years, presence of any radiculopathy, traumatic neuropathy, Central Sleep Apnea syndrome, narcolepsy, COPD, bronchial asthma, chronic alcohol intake, hypertension, coronary heart disease, hyperlipidemia, diabetes mellitus, goiter, chronic renal failure, liver failure, malignancy, or use of neurotoxic drugs.

After applying the exclusion criteria, 86 of 237 selected patients were included. Using the AHI, the participants were divided into a control group (AHI ≤5) (n=40) and OSA group (AHI >5) (n=46). Age, sex, body mass index (BMI), Epworth Sleepiness Scale were measured. Hypoxia parameters including the lowest oxygen saturation (min SaO_2), total sleep duration with oxygen saturation <90% (ST_{90}), percentage of cumulative time with oxygen saturation <90% (CT_{90}), 3% oxygen desaturation index (ODI), and sleep time were calculated and recorded from the patients' PSG records. The participants were further subdivided according to ST_{90}, CT_{90}, min SaO_2, and ODI.

This study was exempted from the requirement for ethics committee approval from the institutional review board of our university due to its retrospective nature.

Polysomnography

All participants underwent PSG using a computerized PSG device in the sleep laboratory (E series, 44 channels; Compumedics, Victoria, NSW, Australia). The following parameters were documented during the PSG study (16 channels): four-channel electroencephalogram, electrooculogram, submental and leg electromyogram, electrocardiogram, nasal airflow using a nasal pressure cannula, airflow at the nose and mouth (thermistors), chest and abdominal respiratory movements, oxygen saturation (pulse oximetry), snoring microphone, and body position. All studies were interpreted by a sleep specialist (pulmonologist) who was blinded to the participants' characteristics. Apnea, hypopneaand sleep staging were defined and performed according to standards of the American Academy of Sleep Medicine criteria (14). The ST_{90} was recorded in minutes, and min SaO_2 and CT_{90} were recorded as percentages. The min SaO_2 value was the lowest oxygen saturation during sleep.

Nerve Conduction Studies

NCSs of bilateral tibial, peroneal, and sural nerves were performed using an electromyography device (Neuropack M1 MEB 2002; Nihon Kohden, Tokyo, Japan). Standardized techniques and procedures were used as described in the guidelines of electrodynamic medicine (15). Filter settings were 3 Hz-10 kHz for the motor NCSs and 20 Hz-2 kHz for the sensory NCSs. During the testing procedures, the room temperature was maintained at an average of 25 °C and skin temperature was maintained at >33 °C in all participants.

Statistical Analysis

The statistical data were evaluated using IBM SPSS Statistics for Windows (ver. 20.0; IBM Corp, Armonk, NY, USA). To test the homogeneity of variances, which is a prerequisite of parametric tests, Levene's test was used. The assumption of normality was tested via the Shapiro-Wilk test. To compare differences between the characteristics of patients with OSA and controls, the Student's t-test was used when the parametric test prerequisites were met, and the Mann-Whitney U test was used when such prerequisites were not met. The chi-square test was used to determine the relationships between two discrete variables. Values were determined through the Monte Carlo simulation method when the expected sources were less than 20% to include such sources in analyses. Age and BMI were determined as covariates (to be excluded), and groups were compared by a covariance analysis (Table 1). The relationship between two continuous variables was assessed by Pearson's correlation analyses and Spearmans correlation analyses when the parametric test prerequisites were not met (Table 2). Binary logistic regression analyses were used to reveal the model for the relationship between the independent and dependent variables (Table 3). A p value <0.05 was set for level of significance.

Results

Characteristics of the subjects with OSA and the controls are described in Table 1. Significant differences in age, sex, BMI, the AHI, and the hypoxia parameters were observed among both groups (Table 1). In OSA subjects, peroneal nerve distal motor latency was prolonged and sural Sensory nerve action potential (SNAP) amplitude and velocity were significantly decreased (Table 1). After adjusting for age and BMI, the differences in peroneal nerve motor latency, sural SNAP amplitude, and sural nerve conduction velocity (NCV) of the two groups remained significant (Table 1). Univariate analyses revealed a significant mild to moderate correlation

Table 1. Comparison of the characteristics of the study participants with Obstructive Sleep Apnea and control subjects. Age- and body mass index-adjusted analyses

		Control	Obstructive Sleep Apnea	p	Adjust BMI and Age‖
		n=40	n=46		p
Age (years)		44.4±13.9	54.7±12.4	0.001†	–
Sex	Female	22 (55%)	12 (26.1%)	0.006§	–
	Male	18 (45%)	34 (73.9%)		
Epworth Sleepiness Scale		6.7±6.3	10.8±0.5	0.001‡	0.001
Body mass index (kg/m^2)		25.8±3.4	32.3±5.3	0.001‡	–
Apnea-hypopnea index (events/h)		1.5±1.3	23.3±20.6	0.001†	0.001
Total sleep time (min)		447.1±22.9	440.6±40.5	NS‡	NS
Oxygen desaturation index (%)		3.1±1.4	4.9±1.6	0.001‡	0.001
ST_{90} (min)		1.3±3.3	23.3±47.5	0.001‡	0.001
CT_{90} (%)		0.3±0.7	5.6±12.2	0.01‡	0.01
Minimum oxygen saturation (%)		90.7±4.7	81.2±7.8	0.001‡	0.001
Tibial motor nerve latency (ms)		4.2±0.7	4.3±0.91	0.001‡	0.001
Tibial CMAP amplitude (mV)		15.4±6.2	11.8±4.5	0.040‡	0.01
Tibial motor nerve velocity (m/s)		48.1±4.03	45.1±8.3	NS‡	NS
Peroneal motor nerve latency (ms)		3.9±0.5	4.2±0.7	0.001‡	0.001
Peroneal CMAP amplitude (mV)		10.3±4.3	6.9±2.9	NS‡	NS
Peroneal motor nerve velocity (m/s)		50.9±4.9	49.3±5.4	NS‡	NS
Sural nerve latency (ms)		2.3±0.3	2.2±0.3	0.01‡	0.01
Sural SNAP amplitude (mV)		19.5±9.04	14.2±8.3	0.04‡	0.01
Sural nerve velocity (m/s)		55.01±6.2	50.6±12.2	0.001†	0.001

CMAP: Compound muscle action potential, CT_{90}: Percentage of cumulative sleep time with oxygen saturation <90%, SNAP: Sensory nerve action potential, ST_{90}: Total sleep time with oxygen saturation <90%

*Data are means ± standard deviations, numbers of subjects (%)

†NS: nNt significant (p>0.05)

†Mann-Whitney U Test

‡Student's t-test

§Fisher Exact chi-square test

‖Covariance analysis

Table 2. Correlation between hypoxia parameters and peripheral nerves

		Tibial motor latency	Tibial CMAP amplitude	Tibial motor velocity	Peroneal motor latency	Peroneal CMAP amplitude	Peroneal motor velocity	Sural sensory latency	Sural SNAP amplitude	Sural sensory velocity
ODI	r	0.290	-0.468	-0.328	0.329	-0.421	-0.221	0.101	-0.247	-0.365
	p	0.007‡	0.000†	0.002‡	0.002‡	0.000†	0.041‡	NS‡	0.022‡	0.001†
ST_{90}	r	0.081	-0.183	-0.283	0.105	-0.400	-0.078	-0.112	-0.236	-0.298
	p	NS‡	NS‡	0.008‡	NS‡	0.000‡	NS‡	NS‡	0.029‡	0.005‡
CT_{90}	r	0.076	-0.159	-0.272	0.072	-0.378	-0.074	-0.121	-0.215	-0.269
	p	NS‡	NS‡	0.011‡	NS‡	0.000‡	NS†	NS‡	0.046‡	0.012‡
min O_2	r	-0.144	0.339	0.324	-0.255	0.467	0.120	0.085	0.203	0.286
	p	NS‡	0.001†	0.002‡	0.018‡	0.000†	NS†	NS†	NS†	0.008‡

CMAP: Compound muscle action potential, CT_{90}: Percentage of cumulative sleep time with oxygen saturation <90%, min O_2: Lowest oxygen saturation, ODI: Oxygen desaturation index, SNAP: Sensory nerve action potential, ST_{90}: Total sleep time with oxygen saturation <90%

†NS: Not significant (p>0.05) (n=86)

†Pearson correlation

‡Spearman correlation

Table 3. Factors affecting peripheral nerves in Obstructive Sleep Apnea

Model		Unstandardized coefficients		Standardized coefficients		
		B	Standard error	Beta	t	p
ST_{90} (min)	Peroneal CMAP amplitude (mV)	–2.655	0.960	–0.293	–2,766	0.007
	Sural sensory latency (ms)	–41.721	18.491	–0.343	–2.256	0.027
	Sural sensory velocity (m/s)	–1.880	0.917	–0.319	–2.050	0.044
CT_{90} (%)	Tibial motor velocity (m/s)	–0,423	0.226	–0.211	–1.868	NS
	Peroneal motor latency (ms)	–2.764	1.638	–0.184	–1.688	NS
	Peroneal CMAP amplitude (mV)	–0.591	0.256	–0.255	–2.306	0.024
	Sural sensory latency (ms)	–14.087	5.016	–0.453	–2.808	0.006
	Sural sensory velocity (m/s)	–0.533	0.241	–0.353	–2.210	0.030
min SaO_2 (%)	Tibial motor velocity (ms)	0.404	0.187	0.231	2.161	0.034
	Peroneal CMAP amplitude (mV)	0.643	0.213	0.319	3.016	0.003
	Sural sensory latency (ms)	9.340	4.081	0.345	2.288	0.025
	Sural sensory velocity (m/s)	0.332	0.196	0.252	1.695	NS
ODI (%)	Tibial CMAP amplitude (mV)	–0.094	0.032	–0.301	–2.910	0.005
	Peroneal motor latency (ms)	0.486	0.280	0.174	1.737	NS
	Peroneal CMAP amplitude (mV)	–0.097	0.046	–0.224	–2.111	0.038

CT_{90}: Percentage of cumulative sleep time with oxygen saturation <90%, min SaO_2: Lowest oxygen saturation, ODI: Oxygen desaturation index, ST_{90}: Total sleep time with oxygen saturation <90%, CMAP: Compound muscle action potantial

†NS: Not significant (p>0.05)

*Data are correlation coefficients and 95%

between the NCS results and the hypoxia parameters (Table 2). After adjusting for confounding factors, multiple logistic regression analyses revealed that prolonged sural sensory latency [odds ratio OR: 0.018, 95% confidence interval (CI): 0.001-0.550, p=0.021] and slowing of sural conduction velocity (OR: 0.816, 95% CI: 0.982-0.031, p=0.031) were independently associated with OSA. Furthermore, logistic regression analyses revealed that the ST_{90}, CT_{90}, min SaO_2, and ODI were independently affecting the NCSs (Table 3).

Discussion

This study suggested that OSA and intermittent hypoxia have significant effects on motor and sensory peripheric nerve function. The peroneal nerve distal latency was prolonged, sural SNAP amplitude reduced, and sural nerve velocity decreased in the OSA group (Table 1). NCSs results showed a significant correlation with the hypoxia (Table 2). The hypoxia parameters were independent factors associated with nerve conduction abnormalities (Table 3). This subclinical peripheral neuropathy is therefore related to severe OSA and intermittent hypoxia seems to cause axonal and demyelinating neuropathy.

Our study shows a relationship among axonal neuropathy, hypoxia parameters and nerve conduction in OSA patients, which is consistent with previous reports (9,10,13). These studies also reported that subjects with severe OSA, min SaO_2 ≤80%, and ST_{90} have lower amplitude for sensory and mixed nerve action potentials, and that sural nerve velocity is slower in OSA patients (8,9). Similar to our study, hypoxia-associated axonal degeneration and less frequent demyelination were reported in COPD subjects in another study (16). These pathophysiological changes in nerve damage are more functional than structural because sleep apnea treatment revealed that the impaired nerve function was partially reversible (10,17).

In contrast to our study, Evlice et al. (12) described a decrease in tibial CMAP amplitude and slower tibial NCV in the OSA group, but they found no correlation among the severity of OSA, min SaO_2, and neuropathy. The patients with OSA were older compared to our study and the authors only used the min SaO_2 saturation as a hypoxia parameter (12).

The etiology of hypoxia-related diseases is complex. The episodic upper airway obstruction in patients with OSA results in hypoxia and hypercapnia. Hypoxia causes oxidative stress, sympathetic activation, metabolic dysfunction, systemic inflammation, endothelial dysfunction, and arterial disease together with pathological changes in morphology (2,18,19).

Electrophysiological abnormalities are reported in approximately 95% of subjects with COPD associated with hypoxia (4,5). The pathophysiology of the nerve conduction abnormalities in patients with OSA is not exactly known. There are several possible explanations for the association between neuropathy of the peripheral nerve and OSA. Oxidative stress plays an important role in hypoxia-induced neuropathy. Endoneurial

hypoxia causes increased intercapillary distance resulting from nerve edema (7,20). The nerve capillary basement membrane thickens and endothelial cell hyperplasia and hypertrophy occur in hypoxic neuropathy. These microvascular angiopathic changes inhibit transport of nutrients and oxygen, altering nerve function and structure and predispose the patient to narrowing of the capillary lumen and vascular occlusion (6,21). In addition, the high-frequency intermittent hypoxia associated with OSA is characterized by a reoxygenation and hypoxemia cycle similar to ischemia-reperfusion injury and generates oxidative stress and reactive oxygen species. During severe hypoxemia, the ischemia and reperfusion sequence leads to the development of tissue acidosis, while intracellular sodium and calcium accumulation lead to sarcolemma damage (22,23). Furthermore, an excitotoxicity mechanism mediated by excitatory amino acids has been reported in hypoxic central nervous system damage. This excitotoxicity is thought to be related to oxidative stress-induced energy metabolism, leading to neurodegeneration (24,25). Last, hypoxic nerves develop resistance to ischemic conduction block (RIBC) due to reduced energy requirement and an increased efficiency of anaerobic glycolysis (26). RIBC is thought to be partially reversible with treatment (10). Chronic severe intermittent hypoxia exposure often results in RIBC, leading to axonopathies. RIBC is a result of an adaptive mechanism that depends on a critical threshold of nocturnal oxygen desaturation and microvascular disorders (10,26). The combination of changes in OSA associated hypoxia results in a high susceptibility to peripheral nerve injury.

The strength of our study is that we have excluded patients with risk factors that cause neuropathy and evaluated detailed hypoxia parameters. Nevertheless, there are limitations of this work included its retrospective design and single-center analysis. Hyperinsulinemia combined with insulin resistance states, such as obesity, may contribute to nerve dysfunction (6). In our study, we did not exclude subjects with BMI ≥30 kg/m^2. But when we adjusted for age and BMI, the results were persistent. Although our study excluded subjects with diabetes, hyperinsulinemia and insulin resistance were not evaluated. Another limitation is that we did not include upper extremity NCS, only lower extremity NCS.

In conclusion, our study revealed that OSA and associated hypoxia affect both motor and sensory nerve conduction, revealing that subclinical peripheral neuropathy is related to OSA. The severity of OSA and severe intermittent hypoxia may cause axonal and demyelinating neuropathy. Future studies comparing the results of our nerve conduction study with oxidative stress and hypercapnia are necessary to provide better insight into the pathophysiology of neuropathy in OSA. These studies should be multicentered, and prospective with a larger OSA patient population.

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Ethics

Ethics Committee Approval: This study was deemed to be exempt from the requirement for informed consent by the Institutional Review Board of University due to its retrospective design. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Oral informed consent was taken from all the participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Desing: A.Y.A, S.A., Data Collection or Processing: A.Y.A., S.A., Analysis or Interpretation: A.Y.A., Literature Search: A.Y.A., Writing: A.Y.A.

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