Serum Neuron-Specific Enolase (NSE) and Homocysteine Levels in Obtructive Sleep Apnea Syndrome (OSAS)

Obstrüktif Uyku Apnesi Sendromu (OUAS)'nda Serum Nöron-Spesifik Enolaz (NSE) ve Homosistein Düzeyleri

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ABSTRACT Objective: Presence of a biochemical marker of cerebral injury would be of great benefit in obstructive sleep apnea syndrome (OSAS) to screen for even small brain damage and to monitor efficacy of therapy. The aim of this study was to evaluate whether two different parameters in serum, neuron-specific enolase (NSE) and homocysteine, can be used to detect even subtle levels of cerebral injury in OSAS patients. **Material and Methods:** We studied 38 patients with OSAS and 30 control subjects with an apnea-hypopnea index (AHI) less than five events per hour. All were evaluated by full-night polysomnography, and in the following morning, serum levels of NSE and homocysteine levels were measured using standard techniques. **Results:** The AHI in OSAS group was 39.2 ± 13.8 (mean ± SD) AH/h. Serum NSE levels were significantly higher in OSAS group (12.3 ± 5.0 ng/ml) than in the control group (8.2 ± 1.9 ng/ml; p< 0.01). No significant difference was detected between the groups with regard to serum homocysteine levels (14.1 ± 6.3 v 14.6 ± 4.8 μmol/L; p> 0.05). **Conclusion:** Elevated serum NSE levels were much more correlated with the severity of OSAS, whereas homocysteine levels were in normal range in these OSAS cases who were otherwise healthy. We believe that there is a need for more sensitive biochemical markers and methods for detecting small cerebral injury in patients with sleep apnea syndrome.

Key Words: Biological markers; brain ınjuries; homocysteine; phosphopyruvate hydratase; sleep apnea, obstructive

ÖZET Amaç Obstrüktif uyku apne sendromu (OUAB) ile ilişkili olası serebral hasarı işaret edebilecek bir biyokimyasal belirteç varlığı tarama ve tedavi etkililiğinin monitörizasyonunda faydalı olacaktır. Bu çalışmanın amacı serumdaki iki farklı parametre olan nöron spesifik enolaz (NSE) ve homosisteinin OUAS hastalarında subklinik düzeylerdeki serebral hasarın tespit edilmesine yönelik kullanılıp kullanılamayacağının araştırılmasıdır. **Gereç ve Yöntemler:** OUAS tanılı 38 hasta ve apne-hipopne indeksi (AHİ) saatte beşden az olan 30 kontrol olgusu çalışmaya alındı. Hepsi tüm gece polisomnografi ile değerlendirildi ve ertesi sabah standart teknikler kullanılarak NSE ve homosistein serum düzeyleri ölçüldü. **Bulgular:** OUAS grubunda AHİ 39.2 ± 13.8 (ortalama ± SD) idi. OUAS grubundaki serum NSE düzeyleri (12.3 ± 5.0 ng/ml) kontrol grubundan (8.2 ± 1.9 ng/ml; p< 0.01) anlamlı olarak yüksekti. Gruplar arasında serum homosistein düzeyleri bakımından anlamlı fark bulunamadı (14.1 ± 6.3E karşılık 14.6 ± 4.8 μmol/L; p> 0.05). **Sonuç:** Serum NSE düzeylerindeki artış OUAS şiddetiyle çok daha fazla ilgiliyken homosistein düzeyleri eşlik eden hastalığı olmayan olgularda normal aralıktaydı. Bu veriler OUAS'lı olgularda küçük serebral hasarın belirlenmesine yönelik daha duyarlı biyokimyasal belirteç ve yöntemlere ihtiyaç duyulduğunu düşündürmüştür.

Anahtar Kelimeler: Biyolojik belirleyiciler; beyin yaralanmaları; homosistein; fosfopiruvat hidrataz; uyku apnesi, tıkayıcı

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Sleep-disordered breathing comprises upper airway resistance syndrome, obstructive sleep apnea, central apnea and central hypoventilation. Among these disorders, obstructive sleep apnea syndrome (OSAS) has been investigated extensively for its associations with cardiovascular complications and thromboembolic events with consecutive ischemic stroke. Cerebral ischemia is one of the major risks for patients with OSAS.[1]

OSAS is a condition characterized by recurrent disturbances of breathing during sleep with repetitive apneas and hypopneas due to intermittent narrowing or occlusion of the upper airway. These respiratory events are accompanied by hypoxia, arousals from sleep and bursts of sympathetic nervous system activity that trigger surges in blood pressure and heart rate.[2] OSAS is also associated with increased platelet adhesiveness, vascular endothelial dysfunction and early signs of atherosclerosis that put patients at increased risk for vascular events including stroke.[3-5] Repetitive nocturnal hypoxemia, negative intrathoracic pressure, sympathetic activation and arousals experienced by OSAS patients are associated with an activation of a number of neural, humoral, thrombotic, metabolic and inflammatory mechanisms. Increased sympathetic activity with elevated pulse rate, sharp swings of arterial blood pressure and cerebral blood flow, disturbances in endothelial function, particularly of nitric oxide synthetase and endothelin pathways, prothrombotic changes with increased factor VII clotting activity, increased platelet activation and aggregation, increased inflammation with elevated levels of fibrinogen, C-reactive protein, inflammatory cytokines and adhesion molecules, and increased oxidative stress related to intermittent hypoxia and normoxia are possible pathophysiological mechanisms linking OSAS with stroke.[6,7] They all may be responsible for onset or rapid progression of stroke during sleep in the patients with OSAS.

The evidence that OSAS might result in cellular damage in the central nervous system is noteworthy. The damage is not seen universally and may be subclinical, remaining undetected for a long time before symptoms manifest. The anatomical and functional extend of stroke can be readily determined through clinical examination and radiological imaging techniques, but majority of the brain is intellectually silent and there are inherent difficulties with the detection of more subtle forms of cerebral injury.

In recent years, several techniques have been developed to measure levels of various biochemical markers to evaluate neuronal injury such as neuron-specific enolase (NSE), creatine kinase BB, myelin basic protein, glial fibrillary acidic protein, interleukin-6, transforming factor-ß, and S-100ß protein.[8] Brain cells contain a number of glycolytic enzyme enolases, and NSE constitutes 75% of total enolase subunits. It is predominantly found in neurons where it is located in the cytoplasm and at low concentrations in neuroendocrine cells. Serum levels increase following head injury, infarction, systemic anoxia and various other insults to central nervous system.[9-13]

Since the pioneering observation of McCully[14] in infants with inborn errors of metabolism, linking elevated levels of the non-protein, sulfur-containing amino acid homocysteine in the plasma with vascular diseases, many clinical and epidemiologic studies have shown a clear correlation between mildly elevated total blood homocysteine concentrations and premature coronary artery disease, peripheral artery diseases, stroke, or venous thrombosis. When strong associations among OSAS, cardiovascular morbidity, and homocysteine levels are considered, it might be possible to link cerebrovascular events with serum homocysteine level in patients with OSAS.

Therefore, it would be useful to have some rapid and simple blood tests that could indicate brain damage in OSAS patients, in order to establish the diagnosis and prognosis, and to guide the therapeutic procedures. The aim of this study was to evaluate whether two different parameters in serum, NSE as a biochemical marker of cerebral injury, and homocysteine as a serologic marker of increased cerebrovascular risk, could be used to detect even subtle levels of cerebral injury in OSAS patients without a previous history of neurological

cerebrovascular event and with normal neurological examination.

MATERIAL AND METHODS

Clinical and laboratory evaluations were conducted in 68 participants who were referred to the sleep laboratory for an assessment of OSAS. None of the patients had a definite history of previous neurological events, hypertension and/or cardiac or peripheral vascular diseases. Patients who participated in the study underwent a detailed cardiac and neurological examination. Patients with a previously documented or clinically evident brain infarction, hemorrhage, head trauma, central nervous system (CNS) infection within six months before admission or with a CNS tumor were excluded from the study. Hypertensive patients and/or patients with risk factors for cardiovascular disease such as high total cholesterol and low density lipoprotein (LDL) cholesterol, and high triglyceride levels were also excluded from the study. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height.

The study was approved by the institutional Ethics Committee, and study was performed in accordance with the guidelines of declaration of Helsinki. Before enrollment, all subjects gave their written informed consent.

SLEEP STUDY

Overnight polysomnography (PSG) was performed in all patients by a computerized system (Compumedics; Australia) and included the following variables: electrooculogram (two channels), electroencephalogram (four channels), electromyogram of submental muscles (one channel), electromyogram of the anterior tibialis muscle of both legs (two channels), electrocardiogram and airflow (with a nasal cannula). Chest and abdominal respiratory efforts (two channels) were recorded using inductive plethismography, and arterial oxyhemoglobin saturation (SaO_2: one channel) was measured using pulse oximetry with a finger probe. The record were obtained at a paper speed of 10 mm/s, and sleep stages were scored according to the standard criteria of American Academy of Sleep Medicine.[15] Arousals were scored according to accepted definitions.[16] Apneas were defined as complete cessation of airflow for $^{3}10$ seconds. Hypopneas were defined as reduction of >50% in one of three respiratory signals, airflow signal or either respiratory or abdominal signals of respiratory inductance plethysmography, with an associated ≥ 3% fall in oxygen saturation or an arousal. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Participants with AHI <5 were included in the control group. Those with AHI $^{3}5$ were considered as OSAS patients.

BLOOD PARAMETER ASSAYS

Fasting blood samples were taken from all subjects between 07:00 AM and 08:00 AM. Blood samples were immediately sent to the hospital laboratory. Serum homocysteine levels were measured using Chromsystems HPLC with Agilent 1100 series fluorescence detector. Normal range was considered as 5-14 μmol/L for homocysteine levels. NSE was determined by radioimmunassay (RIA) method using human NSE as a standard and antiserum raised against human NSE. A NSE level below 12.50 $\mu g\ l^{-1}$ was considered as normal.

STATISTICAL ANALYSIS

Means and standard errors of measurement (SEM) were determined for continuous variables and percentage for categorical variables. Differences between two groups were analyzed using Man Whitney-U test. Categorical data were analyzed by χ^2 with Fisher Exact Probability test. The correlations were analyzed with Spearman's correlation coefficient. All statistical analyses were carried out using a statistical software (SPSS, version 11.0 for Windows; SPSS Inc; Chicago, IL). Differences were considered significant at $P< 0.05$.

RESULTS

After 67 subjects underwent PSG, 37 were considered to have OSAS. OSAS was not considered in 30 subjects and they were enrolled as control subjects. The control subjects were age and BMI matched. The demographic and clinical data of two groups are presented in Table 1. Serum NSE levels

were significantly higher in OSAS group when compared to control group (p= 0.001). No significant difference was detected among the groups with regard to serum homocysteine levels (Table 1). High NSE levels (>12 micromol/liter) were found in 16 patients (42.1%) in the OSAS group with severe hypoxemia, and in one patient (33.3%) in the control group (p< 0.001) (Figure 1). When we evaluated the correlation between the serum NSE level and AHI as a severity measure of OSAS, NSE levels were found positively correlated with the severity of OSAS (r= 0.37, p= 0.02) (Figure 2) and it was also positively correlated with AHl when al lsubjects were considered (r= 0.44, p< 0.001) (Figure 3). There was no correlation between serum homocysteine levels and AHI in OSAS or control groups.

DISCUSSION

Several epidemiological studies showed that OSAS had a high frequency in general population with a prevalence of 2-4%.[17] Nine to 15% of men and 4-9% of women were estimated to have OSAS between 30 and 60 years of age.[18] Alterations in cerebral metabolism, neurological deficits, subtle neuropsychological dysfunction and memory impairment are frequent in OSAS patients.

TABLE 1: The demographic and clinical data of study groups.

Median ± SD (min/max)	OSAS group (n= 37)	Control group (n= 30)	p value
Age (years)	47 ± 8.38 (29/61)	42 ± 6.77 (32/62)	0.08
BMI (kg/m²)	28.4 ± 2.72 (21.8/35.1)	28.2 ± 3.15 (21.8/35.1)	0.83
AHI	37 ± 11 (19/64)	1. ± 1.33 (0/4)	0.001
NSE (ng/ml)	11.6 ± 5.13 (4/23.3)	7.6 ± 1.94 (4.8/12.8)	0.001
Homocysteine (µmol/L)	12.1 ± 6.38 (5.3/33.7)	13.1 ± 4.83 (10/28.5)	0.27
Sex: M/F	27/10	23/7	0.47
Smoking (+/-)	22/15	16/14	0.39

OSAS: obstructive sleep apnea syndrome, BMI: body mass index, AHI: apnea-hypopnea index, SD: standard deviation

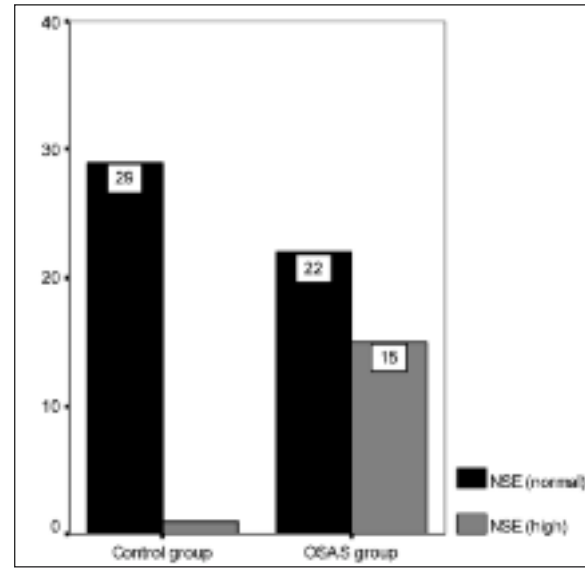

FIGURE 1: High NSE levels was found highly frequent in OSAS group than control group.

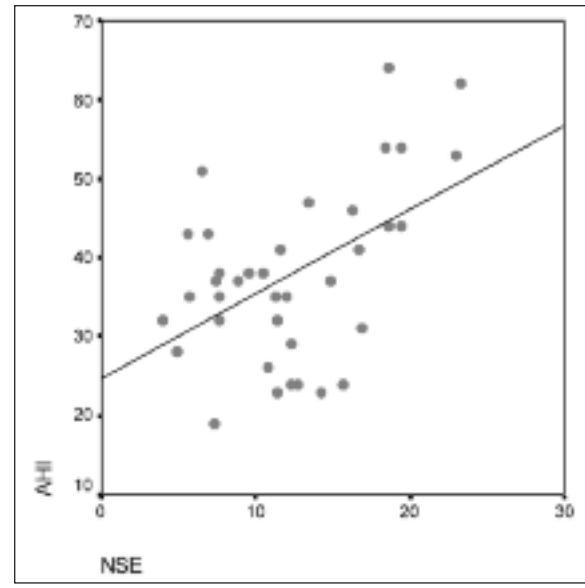

FIGURE 2: Simple correlation between serum NSE levels and AHI in OSAS group (n= 37). NSE levels were positively correlated with AHI in OSAS group (r= 0.37, p= 0.02).

Whether the neurocognitive deficits are a product of sleep fragmentation and sleepiness or relate more to neural damage due to different intermittent hypoxia is unclear at the present time.[19] These deficits may be mediated through excessive daytime sleepiness associated with sleep apnea however, even after adequate therapy for sleep apnea, some neurocognitive deficits such as

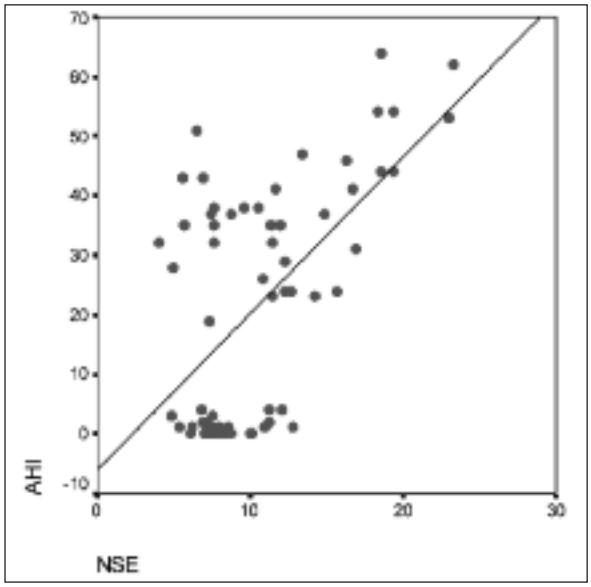

FIGURE 3: Simple correlation between serum NSE levels and AHI in all subjects (n= 67). NSE levels were positively correlated with AHI in all subjects (r= 0.44, p< 0.001).

impairment in executive function and manual dexterity can still persist. Therefore, it is possible that the residual deficits may be related to repeated exposure to hypoxia and cerebral hemodynamic perturbation causing structural changes in the brain. The evidence indicating that OSAS might result in cellular damage in the CNS is noteworthy. Neuropathological, neuropsychological, and metabolic impairments were detected by neurophysiological and psychological assessments and neuroimaging.[20-25] The damage, however, is not seen universally and may be subclinical, remaining undetected for a long time before symptoms manifest. Therefore, a biochemical marker indicating cerebral injury would be of great benefit in OSAS.

Several cerebrospinal fluid (CSF) markers, including S-100ß protein and NSE, may serve as sensitive markers of the extension of brain damage. NSE is an isomer of the glycolytic enzyme enolase existing in all neuroendocrine tissues, but its γ isoform is predominantly neuronal.[26] Studies concerning CSF concentrations of S-100ß protein and NSE in patients with neurological lesions have indicated a quantitative relationship between the degree of cell damage in the CNS and concentration of these proteins in CSF.[27,28] In most studies, these substances can only be measured in the CSF, therefore, potential noninvasive serum biochemical markers would be of particular value in clinical practice to screen small diffuse brain damage. Clinically, increased serum levels of NSE have been found soon after small infarcitions and transient ischemic attacks.[12,13]

In our study, serum NSE levels were significantly higher in OSAS group when compared to the control group, and NSE levels were positively correlated with the severity of OSAS. Although these results support NSE as a marker of subtle cerebral injury, they are inconsistent with previous reports in the literature. Jordan et al. have recently investigated in NSE, S100B, and beta-trace proteins as biochemical markers of brain damage in OSAS patients, and observed no difference between controls and patients.[8] In another study, Braga et al measured NSE and S100B in a larger group of patients with OSAS and they observed that S100B levels were significantly higher in patients with OSAS when compared to control subjects, whereas there was no difference for NSE levels.[29] In our study, subgroup analyses showed that 42.1% of the patients (16 cases) had severe hypoxemia in addition to high AHI. Therefore, this may explain our result since it is consistent with the hypothesis of hypoxic ischemic encephalopathy. Another causative factor for high NSE levels in this study may be the long duration of the disease before its diagnosis. Ethnicity can also be considered as a risk factor for sleep-disordered breathing. Thus, we can consider all these factors for the difference observed between our study and others.

Previous studies suggested that OSAS might be an important risk factor for stroke. Whether the relation between the syndrome and stroke is independent of confounding risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, and smoking, is unclear. In a recent study, the incidence of stroke was reported as 3.48% in the patients with OSAS whereas it was 1.60% in the control group.[30] The trend analysis revealed a stepwise increase in the risk of stroke with the severity of OSAS and the risk of stroke in the most severe group (AHI >30) was three times higher than that

in the controls. Further studies are needed to establish the true nature and the clinical relevance of the puzzling relationship between OSAS and stroke.

Mechanisms underlying increased risk of stroke are multifactorial and include reduction in cerebral blood flow, altered cerebral autoregulation, and increased platelet aggregation and plasma fibrinogen level. The decrease in arterial blood pressure secondary to more negative intrathoracic pressure and gradual rise in intracranial pressure during apnea results in a decrease in cerebral perfusion pressure. Those changes in cerebral blood velocity during apneic episodes and concomitant alterations of vessel wall tension may lead to chronic strain on the cerebral vessels and formation of atherosclerosis.[31] There are also several hematological mechanisms that may contribute to increased hypercoagulability in patients with OSAS and predispose patients to ischemic and thrombotic stroke. These include increased blood viscosity, high fibrinogen concentrations, and increased platelet aggregation. Erythropoietin production is triggered by hypoxemia and is thought to adversely affect the vascular environment through multiple mechanisms. Although the interaction between OSAS and erythropoietin is somewhat controversial, one recent study demonstrated that severe apneics, unlike mild apneics and controls, have a rise in erythropoietin levels after a few hours of untreated sleep which then normalizes after sleeping with CPAP.[32,33] All these mechanisms support a thrombosis-prone state in patients with OSAS.

Homocysteine is an intermediate amino acid in methionine-cysteine metabolism as it represents a branching point at which it can be remethylated to methionine or converted to cysteine.[34] It was described by McCully in infants with inborn errors of metabolism, as an atherogenic compound that accelerates atherosclerosis.[14] Many clinical and epidemiological studies confirmed that a mild elevation in total plasma homocysteine confers an increased risk for peripheral arterial occlusive disease, coronary artery disease and cerebrovascular disease, similar to other conventional risk factors such as hyperlipidemia or smoking.[35] Assessment of serum homocysteine in patients with OSAS is highly relevant, since thromboembolic and hemodynamic events with consecutive ischemic stroke are possible consequences, and cerebral ischemia is one of the major risks. Therefore, we also measured serum homocysteine, which could be a serologic marker for increased vascular risk. Svatikova and colleagues showed that homocysteine levels were not elevated in OSAS subjects.[36] Lavie et al. similarly did not find an increase in homocysteine levels in otherwise healthy OSAS subjects, although they did find increased levels of homocysteine in OSAS patients with concurrent ischemic heart disease or hypertension.[37] In our study, serum homocysteine levels were in normal range both in patients with OSAS and in the control group. The strength of the present study is that we avoided several common pitfalls while including the patients in the study. Hypertensive patients and/or patients with risk factors for cardiovascular disease were excluded whereas age-BMI matched subjects were included. The only limitation of our study is that homocysteine levels was only measured in the morning hours although there is a marked diurnal variation in homocysteine levels, with peak levels occurring late in the evening.

In summary, the present data indicate that serum NSE levels are significantly elevated in OSAS subjects. As the highest levels were found in severe hypoxemic patients with high AHI, the combined effect of severe OSAS and severe hypoxemia might have enhanced the risk of stroke in this population. Our results, however, are in disagreement with a few previous reports in the literature. In view of the normal serum levels of homocysteine in otherwise healthy, OSAS patients we can speculate that use of this protein as a marker of brain impairment is limited. Several important questions still need to be clarified and further investigations are required, especially in the area of biochemical markers of small cerebral damage in OSAS patients, to monitor progression and efficacy of therapy.

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