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Original Article

Serum norepinephrine and homocysteine levels are correlated with the severity of obstructive sleep apnea hypopnea syndrome

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Abstract: Objective: To investigate the correlation between serum norepinephrine (NE) and homocysteine (Hcy) levels and the severity of obstructive sleep apnea hypopnea syndrome (OSAHS). Methods: Seventy-eight patients (22 with mild disease, 32 with moderate disease, and 24 with severe disease according to the apnea hypopnea index, AHI) with a confirmed diagnosis of OSAHS were recruited for this study from August 2016 to July 2018 at the Zhuji Affiliated Hospital of Shaoxing University. All the patients received a polysomnography examination. The serum NE and Hcy levels were determined using an enzyme-linked immunosorbent assay (ELISA) and compared among the mild, moderate, and severe groups. The correlations between the serum NE and Hcy levels and the severity of OSAHS in the patients were evaluated using the Pearson correlation test. Results: Significant statistical differences were found among the mild, moderate, and severe groups for serum NE and Hcy ($P<0.05$). The serum NE and Hcy levels of the severe group were significantly higher than the levels in the moderate and mild groups ($P<0.05$). There were no significant statistical differences in the systolic pressure among the mild, moderate, and severe groups ($P>0.05$). However, the diastolic pressure in the severe group was significantly higher than the level in the mild group with a significant difference ($P<0.05$); The $LSaO_2$ were 82.57±7.77 (%), 78.79±6.83 (%), and 66.79±6.09 (%) for the mild, moderate, and severe groups respectively with a significant difference ($P<0.05$). There were significant correlations between the serum Hcy and NE levels in the mild, moderate, and severe groups ($P<0.05$). And a negative correlation ($r_{Pearson}$=-0.38, P=0.03) was found between NE and $LSaO_2$ in the moderate group. Conclusion: Serum NE and Hcy levels are elevated with the development of OSAHS and correlate with disease severity.

Keywords: OSAHS, homocysteine, norepinephrine, disease severity

Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS) is the most frequent, clinically-diagnosed sleep apnea disorder. It is caused by intermittent hypoxia due to a repeated partial- or complete-obstruction of the upper airway during sleep. An epidemiological study from Europe found that the incidence rate of OSAHS is 2%-4% in adults [1]. Data from China indicates that the incidence of OSAHS is about 4%, which is similar to the rate in Europe [2, 3]. Zheng [2] also found that every breathing event is associated with tachycardia, elevated blood pressure, and frequent awakening. The incidence of OSAHS is higher in cases with diabetes, obesity, hypertension, dyslipidemia, coronary heart disease and heart failure compared to the healthy population [4]. This result indicated OSAHS may not only be a respiratory disease, but also a manifestation of metabolic disorders, some of which are caused by obesity, especially centripetal obesity.

Homocysteine (Hcy) is a sulfur-containing amino acid which is clinically used as a risk indicator for cardiovascular diseases, especially coronary atherosclerotic heart disease and myocardial infarction. Many studies have pointed out that hyperhomocysteinemia is an independent risk factor for cardio-cerebrovascular disease and is closely related to patient prognosis [5]. However, the correlation between serum Hcy and OSAHS is rarely studied.

Table 1. Serum NE and Hcy comparisons of the mild, moderate, and severe OSAHS groups

Group	n.	NE (ng/mL)		Hcy (μmol/L)	
		Mean ± SD	Median (Range)	Mean ± SD	Median (Range)
Mild	22	4.42±1.58	4.04 (2.12~7.89)	10.89±2.36	10.73 (6.87~19.12)
Moderate	32	6.08±1.67	6.06 (3.21~10.12)	12.75±2.88	12.63 (7.56~19.11)
Severe	24	9.33±3.02	9.03 (4.32~15.12)	16.33±4.75	16.11 (8.12~26.14)

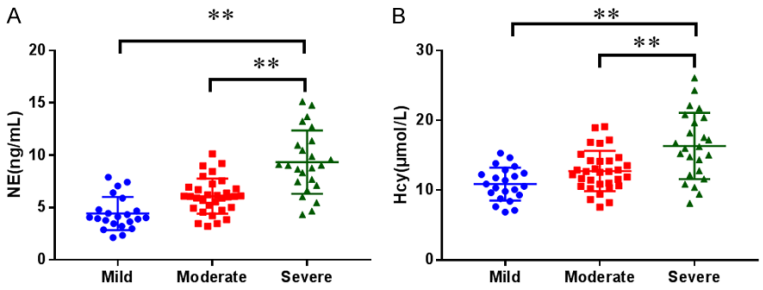

Figure 1. A scatter plot of the serum NE and Hcy level distribution in the mild, moderate, and severe OSAHS groups (A: Serum NE; B: Serum Hcy), **P<0.01.

Table 2. Blood pressure and $LSaO_2$ comparisons of the mild, moderate and severe OSAHS groups

Group	n.	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	$LSaO_2$ (%)
Mild	22	125.7±18.45	76.43±11.44	82.57±7.77
Moderate	32	128.20±17.06	83.17±11.51	78.79±6.83
Severe	24	133.60±17.24	84.54±11.17	66.79±6.09
F		1.23	3.36	34.24
p		0.30	0.04	<0.001

Material and methods

Patients

Seventy-eight patients with a confirmed diagnosis of OSAHS were recruited for this study from August 2016 to July 2018 at the Zhuji Affiliated Hospital of Shaoxing University. Of the 78 cases, 22 were diagnosed with mild disease (the mild group, 5< AHI <15), 32 were diagnosed with moderate disease (the moderate group, 15< AHI <30), and 24 were diagnosed with severe disease (the severe group, AHI >30) according to the apnea hypopnea index, (AHI) [6]. The mean age of the 78 cases was 51.21±11.68, and there were 69 male and 9 female patients in the cohort. All of the patients included in the present study provided a written informed consent. This research related to humans complied with all the relevant national regulations and institutional policies, was carried out in accordance the tenets of the Helsinki Declaration, and was approved by Zhuji Central Hospital's institutional review board.

Polysomnography examination

All the patients received a polysomnography examination in a special sleep monitoring room for at least 7 hours. The electroophthalmic data, the electroencephalograms, mandibular electromyography, chest and abdomen breathing movements, oronasal airflow, electrocardiograms, and the blood oxygen saturation of the fingertip were monitored simultaneously. The sleep apnea hypopnea index (AHI) and the lowest oxygen saturation ($LSaO_2$) were also recorded. All the data were automatically recorded in the sleep detector and stored in the computer.

Serum NE and Hcy examinations

All the patients had 3 ml of fasting venous blood drawn on the morning after their examination. The plasma was separated using 3000 r/min centrifugation for 10 minutes, and the specimens were stored in a refrigerator at -80°C until the next use. The serum NE and Hcy were examined using an enzyme-linked immune assay (ELISA).

Statistical analysis

SPSS 19.0 statistical software (IBM, Armonk, NY, USA) was used for the data analysis. The serum NE and Hcy levels, and the blood pressure and $LSaO_2$ levels were first tested for the normal distribution. If the data were found to

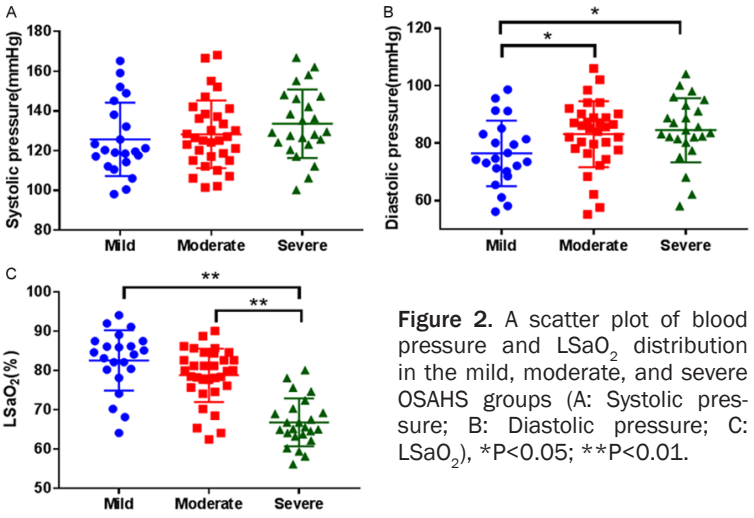

Figure 2. A scatter plot of blood pressure and $LSaO_2$ distribution in the mild, moderate, and severe OSAHS groups (A: Systolic pressure; B: Diastolic pressure; C: $LSaO_2$), *P<0.05; **P<0.01.

Table 3. The correlation of serum NE and Hcy levels and the $LSaO_2$ level

Correlation	$r_{Pearson}$	95% CI	p	Equation
Mild group				
NE and Hcy	0.49	0.08~0.75	0.02	Y=0.73*X+7.68
NE and $LSaO_2$	-0.18	-0.56~0.27	0.43	Y=-0.72*X+86.56
Hcy and $LSaO_2$	-0.24	-0.60~0.20	0.28	Y=-0.66*X+90.57
Moderate group				
NE and Hcy	0.62	0.34~0.79	0.001	Y=1.06*X+6.31
NE and $LSaO_2$	-0.38	-0.65~-0.04	0.03	Y=-1.56*X+88.29
Hcy and $LSaO_2$	-0.02	-0.36~0.33	0.91	Y=-0.05*X+79.39
Severe group				
NE and Hcy	0.63	0.30~0.82	0.001	Y=0.98*X+7.17
NE and $LSaO_2$	-0.16	-0.53~0.26	0.46	Y=-0.32*X+69.74
Hcy and $LSaO_2$	0.03	-0.38~0.43	0.90	Y=0.03*X+66.22

have a normal distribution, they were expressed as the means ± sd and compared using a one-way ANOVA test. The correlations for serum Hcy, NE, and $LSaO_2$ were analyzed using a Pearson correlation test. A Two-tailed P<005 was considered statistically significant.

Results

Serum NE and Hcy examination

The serum levels of NE and Hcy are shown in **Table 1**. A significant statistical difference in serum NE and Hcy levels was found among the mild, moderate, and severe groups (P<0.05). The severe group's serum NE and Hcy levels were significantly higher than of the levels found in the moderate and mild groups (P< 0.05), **Figure 1**.

Pre-bedtime blood pressure and night $LSaO_2$

The systolic pressure differences were not statistically different in the mild, moderate, and severe groups (P> 0.05) (**Table 2**). However, the diastolic pressure in the severe group was significantly higher than it was in the mild group, with a significant statistical difference (P<0.05). The $LSaO_2$ were 82.57±7.77 (%), 78.79±6.83 (%) and 66.79± 6.09 (%) for the mild, moderate, and severe groups respectively, with a significant statistical difference (P<0.05) (**Figure 2**).

Correlations of serum NE, Hcy AND $LSaO_2$

The correlations between the serum NE, Hcy and $LSaO_2$ levels are shown in **Table 3**. There was a significant correlation between the serum Hcy and NE levels for the mild, moderate and severe groups (P<0.05). And a negative correlation ($r_{Pearson}$=-0.38, p= 0.03) was found between the NE and $LSaO_2$ levels in the moderate group (**Figure 3**).

Discussion

The main clinical symptom of OSAHS is chronic intermittent hypoxia caused by repeated upper airway obstruction during sleep. OSAHS is a common chronic sleep respiratory disease [7]. Studies have proved that OSAHS can cause multiple organ damage and is an independent risk factor for cardiovascular disease [8-10], hypertension [3, 11], and diabetes. OSAHS patients usually have recurrent upper airway stenosis and obstruction during sleep and recurrent apnea and hypopnea. Hypoxia and hypercapnia increase the excitability of the sympathetic nerve by stimulating the central nervous system and peripheral chemoreceptors with an increased sensitivity [12]. At the same time, nighttime micro-arousal caused by

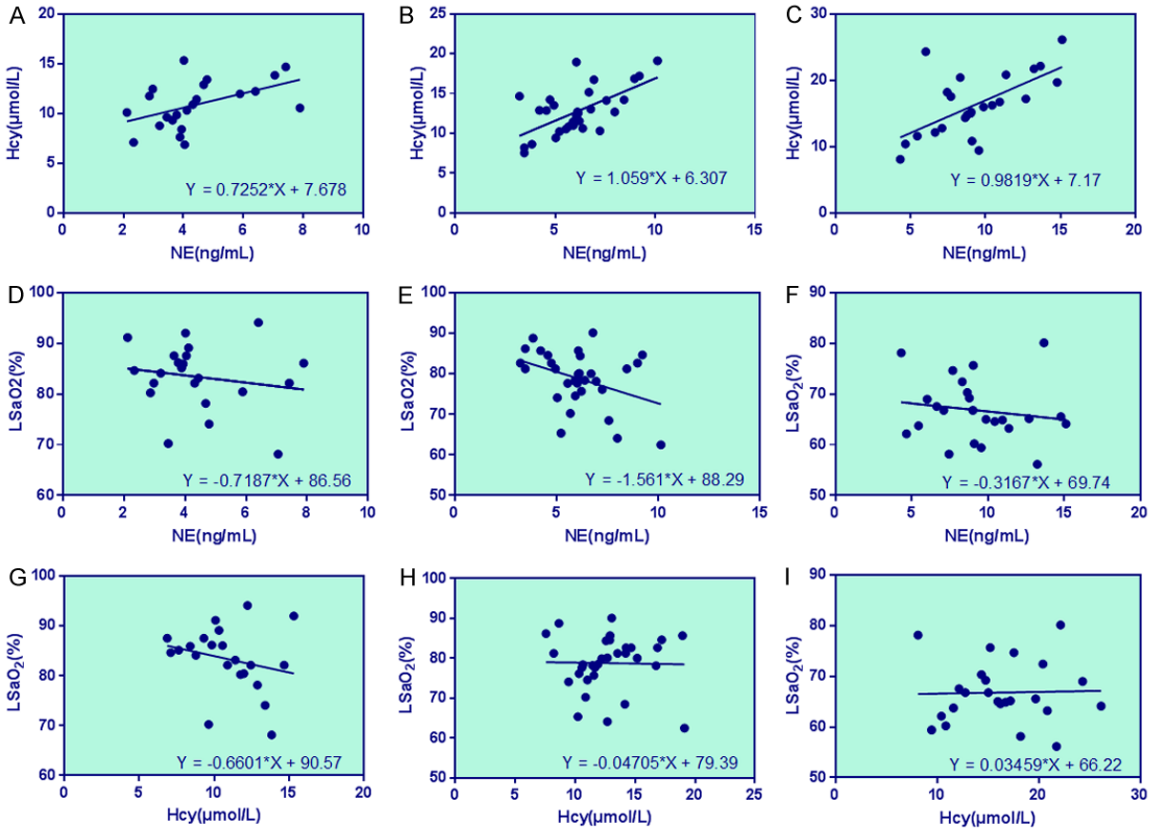

Figure 3. A scatter plot of the Pearson correlation test of the serum NE, Hcy, and $LSaO_2$ levels. (A: Mild group NE and Hcy; B: Moderate group NE and Hcy; C: Severe group NE and Hcy; D: Mild group NE and $LSaO_2$; E: Moderate group NE and $LSaO_2$; F: Severe group NE and $LSaO_2$; G: Mild group; H: Moderate group Hcy and $LSaO_2$; I: Severe group Hcy and $LSaO_2$).

repeated apnea in OSAHS patients can further stimulate the increase of the sympathetic nerve excitation and plasma catecholamine levels, leading to peripheral blood vessel contraction which usually causes elevated diastolic pressure [13, 14]. Intermittent hypoxia caused by repeated apnea and insufficient ventilation during sleep in OSAHS patients can increase sympathetic nerve tension through the carotid body.

NE is a catecholamine derivative derived from the sympathetic adrenal medulla system. The level and changes of NE in the serum can indirectly demonstrate the activity of sympathetic adrenal medulla [15]. In this study, we found that serum NE increased significantly with the severity of OSAHS and was negatively correlated with $LSaO_2$ in the moderate group patients.

Homocysteine (Hcy), a metabolite of methionine, is a risk factor for cardiovascular disease [16, 17]. Several studies had evaluated the serum level of Hcy in OSAHS patients and found that plasma Hcy was usually elevated compared to the healthy controls [18-20]. However, the correlation between serum Hcy and OSAHS severity was inconclusive. In our present work, we found that the serum Hcy level of the severe group was significantly higher than the Hcy levels in the moderate and mild groups. This indicated that the higher the serum Hcy concentration, the more severe the disease.

In conclusion, serum NE and Hcy levels may play an important role in the pathogenesis of OSAHS and vary with the severity of the disease, which is useful for the early diagnosis and early intervention of OSAHS.

Disclosure of conflict of interest

None.

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