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Serum S100B: A possible biomarker for severity of obstructive sleep apnea

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) is characterized by upper airway collapsibility and intermittent hypoxia (IH) during sleep. It has neurological complications and it has been associated with morbidity and mortality. Increased serum levels of S100B protein indicates brain injury. Early detection of possible complications of OSA patients could improve management of the disease.

Study objective: Measurement of serum S100B protein in OSA patients with correlation to the severity of the disease.

Patients and methods: Fifty five OSA patients (24 females; 43.6% and 31 males; 56.4%) and 34 control individuals (17 females; 50% and 17 males; 50%) had a sleep apnea monitoring using the SAM equipment, Inter care technologies, model 100, USA, and S100B serum levels were measured after the sleep study at 6.30–7.30 am.

Results: S100B serum levels were higher in patients than controls ($P < 0.001$) and the levels correlated with the apnea/hypopnea index (AHI) ($P < 0.001$), lowest oxygen saturation (LOS) ($P < 0.001$), and oxygen desaturation index (ODI) ($P < 0.001$).

Conclusion: Serum S100B protein was significantly elevated in OSA patients and its serum levels correlated with the severity of the disease. Increased serum S100B could indicat brain injury and could be a potential serum biomarker for detection of early neurological complications in OSA patients that could improve the management and care of these patients.

Introduction

Obstructive sleep apnea (OSA) is characterized by increased upper airway collapsibility during sleep which leads to intermittent hypoxia (IH) [1]. OSA has increased in the general population and it has been associated with complications that may arise mainly from chronic intermittent hypoxia during sleep. IH results in a systemic inflammatory response with increased production of reactive oxygen species and inflammatory cytokines [2]. OSA has been associated with an increased risk for hypertension, atherosclerosis, myocardial infarction [3] and diabetes mellitus (DM) type 2 [1]. Diabetic patients have an increased prevalence of OSA [4]. Diabetic OSA patients show decreased intraepidermal nerve fiber density (IENFD) that indicates early peripheral neuropathy, increased poly ADP ribose polymerase (PARP) activation that indicates increased nitrosative stress and endothelial dysfunction which contribute to the increased occurrence of diabetic foot ulceration [5]. Increased oxidative stress in OSA patients also causes neuro cognitive impairment [6]. Sympathetic overdrive, IH, endothelial impairment and systemic inflammation increase the incidence of renal function impairment and diabetic kidney disease in diabetic OSA patients [7]. Some ophthalmologic complications such as floppy eyelid syndrome, optic neuropathy and papilledema may occur in OSA [8].

Biomarkers are a wide variety of products found in blood, tissues and body fluids. They express both health and disease in proper situations [9]. A useful biomarker should have a high sensitivity and specificity, correlates with the severity of the disease and shows response to treatment [10]. Some biomarkers such as blood

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interleukin (IL) – 6 and IL – 10 showed association with OSA in adults [9]. S100B is a calcium binding protein that is mainly produced by astrocytes [11]. S100B protein is involved in the integrity of the function and structure of the neuronal cell and it is also involved in the control of calcium in the body [12]. S100B protein undergoes renal degradation via the renal proximal tubules and patients with renal insufficiency may show elevated levels of S100B [13]. S100B in nanomolar levels is normal and maintains the integrity of neuronal cells, but in micromolar concentrations may indicate cell injury and impairment [14]. Increased serum S100B, in addition, could indicate glial cell abnormality [15] and may correlate with Parkinson's disease severity [16].

To our knowledge, few studies addressed the association of OSA and S100B protein. This study aimed to investigate whether this protein might be a useful biomarker for severity of OSA.

Patients and methods

Fifty five adult patients of both sexes complaining from OSA presenting to the outpatient clinics of the Suez – Canal University hospital and thirty four matching non complaining individuals were included in the study. All participants were informed about the aim of the study. The current work was approved by the Medical Research Ethics Committee of Faculty of Medicine, Suez Canal University (approval No. 3087). Medical history focusing on symptoms suggestive of OSA, chronic diseases and demographic data were taken. Patients with advanced cardiac disease, renal insufficiency and patients with history of malignancy excluded from the study. All individuals were subjected to physical examination including measurement of neck circumference, body mass index (BMI), cardiac, chest and ENT examination. All individuals had a sleep study with the sleep apnea monitoring; SAM equipment (Inter care technologies, model 100, USA). A flow sensor for detection of apneas and hypopneas, abdominal and thoracic belts for detection of respiratory effort, and a pulse oximetry for the arterial blood saturation and the lowest oxygen saturation were performed. Mild OSA patients had an apnea/hypopneas index (AHI) of 5–15/hour, moderate OSA patients had an AHI of 16–30/hour and severe OSA patients had an AHI of more than 30/hour.

Four cm of venous blood were withdrawn from all participants at 6.30–7.30 am and samples were centrifuged and the serum aliquotes were kept in a – 80 degrees Celsius until measuring serum S100B protein levels using a commercially available ELISA based-kit (R&D Systems, Minneapolis, Minnesota) according to the manufacturer recommendations.

Statistical analysis

PC-ORD version5 software and Statistical Package for the Social Sciences (SPSS) for windows software (version 22.0) were used for statistical data analysis. Chi-square (χ^2), student's *t* and Mann-Whitney *U* (MW) tests were used for comparison. A two-tailed p-value of <0.05 was considered statistically significant. The area under the curve (AUC) of receiver operating characteristic (ROC) was performed under the nonparametric assumption to identify the diagnostic accuracy of S100B in OSA disease. Correlation analysis between the variables was performed via Spearman's correlation coefficient. Stepwise regression analysis was executed to identify which of the predictors are significantly contributing to OSA disease. For multivariate analysis, data profile was checked for outliers and no transformation was required. Two-way agglomerative hierarchical clustering was performed to identify the combination of risk factors with S100B expression level that are the most important to discriminate OSA patients from controls. Flexible Beta method and Sorensen (Bray-Curtis) were adjusted for linkage method and distance measure, respectively, with Beta value of −0.75 to reach the minimum % of chaining. In addition, Principal Components Analysis was run to separate different groups of patients upon similarities and dissimilarities among patients. Ordination graphs were used to visualize patients' data along axes as coordinates in a distance-based biplot according to their resemblances.

Results

Table 1 showed that both study groups were matched for age, sex, and co-morbidities. However, OSA patients had higher BMI ($P < 0.001$) and neck circumference ($P < 0.001$). Table 2 showed that S100B levels were significantly higher in OSA patients compared to controls ($P < 0.001$). Fig. 1 showed that S100B expression levels were significantly higher in OSA patients compared to controls. ROC analysis revealed a high diagnostic value of S100B in OSA disease. The AUC was 0.998 ± 0.003 (95 CI of 0.993–1.00) with

Table 1
Baseline characteristics of the study groups.

	Controls (n = 34)	Patients (n = 55)	P values	OR (95% CI)
Age, yr	45.11 ± 8.83	44.14 ± 9.27	0.626	
<45 years	15 (44.1)	30 (54.5)	0.230	1.0
≥45 years	19 (55.9)	25 (45.5)		0.65 (0.27–1.5)
Gender, %				
Female	17 (50)	24	0.357	1.0
Male	17 (50)	31 (56.4)		1.29 (0.54–3.04)
BMI, kg/m^2	30.6 ± 3.7	35.7 ± 6.4	**<0.001***	
Obesity, %	27 (79.4)	41 (74.5)	0.398	0.75 (0.27–2.12)
NC, cm	37.9 ± 2.1	40.8 ± 3.2	**<0.001***	
Hypertension, %	4 (11.8)	15 (27.3)	0.068	2.81 (0.84–9.34)
Diabetes, %	4 (11.8)	12 (21.8)	0.181	2.09 (0.61–7.11)
Ischemic heart disease, %	0 (0.0)	2 (3.6)	0.379	
AHI, events/h	2 (1.5–3.0)	12 (7–20)	**<0.001***	
Normal	34 (100)	2 (3.6)	NA	
Mild		32 (58.2)		
Moderate		14 (25.5)		
Severe		7 (12.7)		
SaO_2, %	92.2 ± 1.03	58.2 ± 12.6	**<0.001***	
ODI > 4%/h	2 (0–2)	22 (12–36)	**<0.001***	

Data is represented as number (percentage), mean ± SD, or median (quartiles). BMI = body mass index, NC = neck circumference, AHI = apnea/Hypopnea index, SaO_2=oxygen plasma saturation% lowest O2 saturation, ODI = Oxygen desaturation index. Chi square, student's *t*, and Mann-Whitney *U* tests were used. Bold values indicate statistically significant at $P < 0.05$.

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