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Original Article

Association of inflammation and oxidative stress with obstructive sleep apnea in ischemic stroke patients

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ABSTRACT

Objective: The role of obstructive sleep apnea (OSA) in the mortality and further cardiovascular risk in subjects with ischemic stroke remains a contentious issue. Oxidative stress and inflammatory reaction due to OSA have seldom been studied in stable ischemic stroke patients.
Patients/Methods: This cross-sectional, prospective study involved 92 consecutive ischemic stroke patients who were admitted to the Rehabilitation ward. All subjects received polysomnography and laboratory tests for oxidative stress and inflammatory biomarkers, including: C-reactive protein (CRP), interleukin 6 (IL-6), total antioxidant capacity (TAC), and urinary 8-hydroxy-2-deoxyguanosine. Differences in study variables between patients with or without severe OSA were compared, and multivariate linear regression analyses were used to assess the relationship between OSA severity and target biomarkers.
Results: Participants in the severe OSA group were significantly older ($p = 0.002$), had a significantly higher risk of hypertension ($p = 0.021$) and a lower level of CRP ($p = 0.006$). Among the subjects with ischemic stroke and severe OSA, the levels of CRP, IL-6, and TAC were positively correlated with the desaturation index (DI) and the TAC levels were negatively correlated with mean arterial oxygen saturation (SaO_2). Regression analysis results indicated that the TAC levels remained significantly and negatively correlated with mean SaO_2 levels. Moreover, the CRP levels remained significantly correlated with the apnea–hypopnea index and DI after controlling for covariates.
Conclusions: The present study demonstrated that a preferentially adaptive antioxidative response to hypoxia emerges, and the role of OSA with respect to inflammatory reaction is attenuated, in ischemic stroke patients with OSA.

1. Introduction

Obstructive sleep apnea (OSA) is an independent risk factor for ischemic stroke [1]. However, the role of OSA with respect to the mortality and further cardiovascular risk in ischemic stroke patients remains contentious. Sahlin et al. performed a 10-year follow-up study, and indicated that moderate-to-severe OSA in stroke patients is a risk factor of early death, but not for 10-year mortality [2]. Other observational studies suggested that OSA found in stroke patients is a risk factor for stroke recurrence [3,4]. Those studies also associated continuous positive airway pressure (CPAP) nonadherence with a significant increase in new vascular events (especially new ischemic strokes) [5] and a 5-year mortality rate [6]. However, CPAP-noncompliant patients might have problems with general treatment compliance, leading to a more advanced vascular disease [7]. Conversely, Parra et al. performed a randomized controlled trial, which revealed a similar new cardiovascular event and mortality rate at 2-year follow-up between CPAP users and non-users in OSA patients with ischemic stroke [8].

In contrast to the extensive studies on the pathophysiology in middle-aged OSA patients without stroke, oxidative stress and inflammatory reactions due to OSA have seldom been investigated in ischemic stroke patients. Recent studies have reported increased inflammatory biomarkers such as C-reactive protein (CRP) and interleukin 6 (IL-6) in acute ischemic stroke patients with OSA [9–11], which is consistent with the finding in typical middle-aged OSA patients without stroke. Interleukin 6, an atherogenic

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marker, increased commensurately in acute ischemic stroke patients with OSA, and was correlated with oxyhemoglobin desaturation and with the desaturation index in ischemic stroke patients with severe OSA [10]. Previous studies found that the inflammatory response markedly changed over time after acute ischemic stroke [12]. According to another study, in subjects with transient pharyngeal muscle alteration, obstructive apneic events significantly improved in the stable stroke phase [13]. Therefore, whether the findings that increased IL-6 and CRP levels found in acute ischemic stroke patients with OSA still hold true in chronic ischemic stroke patients with OSA remains unclear.

As is well known, atherogenesis is linked to oxidative stress and lipid peroxidation [14]. Other studies found that the severity of OSA was negatively correlated with total antioxidant capacity (TAC) [15] and positively correlated with urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) excretion [16]. Oxidative stress markers such as TAC (defined as ferric reducing antioxidant power) were found to be useful in detecting and monitoring redox imbalance and the CPAP therapy effect in OSA patients without stroke [15]. The 8-OHdG is a modified deoxyribonucleic acid (DNA) base that has been used for evaluation of oxidative DNA damage [17]. However, it is believed that OSA patients with ischemic stroke have not been examined.

The present study investigated how the inflammatory status, oxidative stress biomarkers and severity of OSA are related in stable ischemic stroke patients. Portable cardiorespiratory polygraphy is often used in acute stroke patients who are not stable enough to receive full polysomnography (PSG) in a sleep center. However, patients suffering from acute stroke are especially susceptible to anxiety, poor sleep quality, and insomnia – all of which cannot be assessed by these portable systems. Performing a full PSG in the stable phase of ischemic stroke could avoid the possible effects of acute stroke, with respect to the severity of apnea and the main limitation of portable cardiorespiratory polygraphy; this would enable elucidation of the pathophysiologic role of OSA in these patient groups. The present study also evaluated how the severity of OSA and recurrent ischemic stroke are related.

2. Method

2.1. Participants

This prospective study examined consecutive stable ischemic stroke patients who were admitted to the Rehabilitation ward of the teaching hospital. Study participants were diagnosed as having ischemic stroke, based on a full clinical assessment with detailed neurological examinations and neuroimaging studies. Exclusion criteria were: severely decreased consciousness; previous history of intracranial hemorrhage or malignancy; evidence of overt congestive cardiac failure; liver dysfunction with ascites; chronic obstructive pulmonary disease under steroid treatment; advanced renal disease (chronic kidney disease Stage 3 or higher); unstable medical and neurological conditions such as pneumonia, asthma, severe infection or uncontrolled diabetic mellitus (DM); and patients with central sleep apnea (CSA). All participants had similar physical activity, as they received regular physical therapy, occupational therapy, and speech therapy. Drugs or dietary supplements such as vitamins, which might interfere with the inflammatory or oxidative stress, were prohibited; this excluded regular medication prescribed by the physicians for any underlying diseases.

The study protocol received approval from the local ethics committee, and all participants or their next of kin (when the participant's communication was impaired) gave informed consent.

2.2. Clinical evaluation

Upon admission, a comprehensive history was taken, which included demographic data and the prevalence of risk factors for stroke (i.e., smoking, hypertension [HTN], dyslipidemia, DM, cardiac arrhythmia, previous ischemic stroke). Initial stroke severity, as measured by the National Institutes of Health Stroke Scale (NIHSS) [18], was taken from the relevant medical reports. Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria [19]. Body mass index, neck circumference, Barthel Index (BI) [20], and Epworth sleepiness scale (ESS) [21], which evaluates the propensity to sleep, were determined on the same day of the PSG examination. The BI was widely used for evaluating functional outcomes in stroke patients.

2.3. Polysomnography

Polysomnography was performed using the Embla N7000 (Somnologica, Iceland) at the sleep laboratory from 22:00 to 05:00. The median time interval between stroke onset and the date of PSG study was 2.2 months (IQR 1.2–4.2). This included: six electroencephalography channels (F3-A1, F4-A2, C3-A1, C4-A2, O1-A1, and O2-A2); an electro-oculogram; a chin and bilateral anterior tibial surface electromyogram; an electrocardiogram; nasal and oral airflow sensors (nasal pressure cannula and oronasal thermistor); thoracic and abdominal movement sensors (inductance plethysmography); and an oxyhemoglobin saturation detector (finger pulse oximetry). A recording time of at least 5 h was required to validate the sleep study. Sleep onset latency, sleep efficiency, and the percentage of total sleep time spent in slow-wave sleep and rapid eye movement (REM) sleep was recorded.

Diagnosis of OSA was based mainly on the American Academy of Sleep Medicine Task Force recommendations [22]. Apnea refers to the cessation of airflow for at least 10 s. The respiratory effort is maintained in obstructive apnea, whereas breathing movements are lacking in central apnea. Mixed apnea refers to the cessation of airflow that is initially associated with the absence of respiratory effort and that persists upon resumption of respiratory effort [22]. Hypopnea refers to a reduction of >50% in airflow for at least 10 s, with either an arousal or oxygen desaturation ≥3%. Oxyhemoglobin desaturation index (DI) (ie, number of desaturations per hour of time in bed) was also calculated. Obstructive sleep apnea was diagnosed when >50% of respiratory events were of obstructive or mixed type. Severe OSA was defined as >30 apnea episodes and/or hypopnea episodes per hour of sleep (apnea–hypopnea index [AHI] > 30 events/h). Central sleep apnea was diagnosed when ≥50% of the respiratory events were of the central type.

2.4. Inflammatory and oxidative biomarkers

Samples of peripheral venous blood and urine were collected after the night that PSG was performed at 05:00. Blood was collected in lithium heparin-containing tubes (4.5 mL lithium heparin PST™ II tubes, BD Vacutainer; BD) and BD Vacutainer SST™ II Advance tubes (Becton Dickinson, Heidelberg, Germany), respectively; they were centrifuged for 10 min at 3000 rpm. Samples were immediately separated into aliquots and stored at –80 °C until analysis in the Medical Center Laboratory of the hospital. Total antioxidant capacity was measured by the ferric reducing ability of plasma assay [23] on the Cobas Mira Plus (Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficients of variation were determined to be 2% and 5%; 1% and 3%, respectively, at two levels. Serum CRP was determined by a high-sensitivity assay using a latex aggregation immunoassay (Nanopia CRP, Daiichi Pure Chemicals Co., Ltd.) with a Hitachi 7600-210 analyzer (Hitachi Instruments Engineering Co., Ltd). The method has a lower limit of sensitivity of 0.1 mg/L and inter-assay and intra-assay coefficients of variation of less than 5%. Serum levels of IL-6 were measured with a sandwich enzyme-linked immunosorbent assay (ELISA) by using standard procedures (R&D Systems, Minneapolis, USA). The tests