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Original Article

Moderate-to-severe obstructive sleep apnea is associated with cerebral small vessel disease

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ABSTRACT

Background: Cerebral small vessel disease (SVD) is associated with increased risk of cerebral infarction and hemorrhage. Obstructive sleep apnea (OSA) is known to increase the risk of cerebrovascular disease. This study aimed to investigate the association between cerebral SVD and severity of OSA.
Methods: A total of 170 patients were included from the patient registry at the present Sleep Center; these patients underwent both magnetic resonance imaging (MRI) of the brain and polysomnography (PSG) for suspected OSA. The presence and burden of white matter hyperintensities (WMHs), asymptomatic lacunar infarctions (ALIs), cerebral microbleeds (CMBs), and perivascular spaces (PVSs) were determined by MRI, and their relationships with the apnea–hypopnea index (AHI), as determined by PSG, were investigated.
Results: Among the 170 patients, 25 (14.7%) had high-grade WMHs, 21 (12.4%) had ALIs, 21 (12.4%) had CMBs, and 34 (20.0%) had high-grade PVSs. In the multivariable analysis, after adjusting for factors including age, sex, and other variables for which $p < 0.1$ in univariable analysis (hypertension, diabetes mellitus, previous stroke, minimal SaO_2 and arousal index), moderate-to-severe OSA was associated with high-grade WMHs (odds ratio [OR] 4.72; 95% confidence interval [CI] 1.14–19.47), CMBs (OR 3.47; 95% CI 0.89–15.18), or high-grade PVSs (OR 3.64; 95% CI 1.02–13.01), but not with ALIs. The total SVD score was independently associated with increased AHI ($p = 0.017$), particularly in patients with moderate-to-severe OSA (β [standard error] = 0.448 (0.204), $p = 0.030$].
Conclusion: Moderate-to-severe OSA is positively associated with multiple indicators of cerebral SVD, including WMHs, CMBs, and PVSs.

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1. Introduction

Cerebral small vessel disease (SVD) is characterized by perforation of small arterioles, with pathology that presents as abnormal high/low signal intensities on brain magnetic resonance imaging (MRI), including: white matter hyperintensities (WMHs), asymptomatic lacunar infarctions (ALIs), cerebral microbleeds (CMBs), and perivascular spaces (PVSs) [1]. These indicators of SVD are closely related to the risk of symptomatic cerebral ischemia and/or hemorrhage, post stroke dementia, vascular cognitive impairment, and recurrent and future stroke [2,3].

Meanwhile, obstructive sleep apnea (OSA) has been reported as one of the risk factors for vascular diseases, including stroke [4]. In previous studies of patients with suspected OSA from a community-dwelling population, the presence of nocturnal hypoxia and moderate-to-severe OSA was associated with WMHs and ALIs [5,6]. In contrast, a case-control study that compared patients with OSA and normal, matched control subjects showed no significant correlation between OSA and SVD (WMHs and ALIs) [7]. Moreover, although each SVD can have a somewhat different impact on clinical presentation (CMBs for cerebral hemorrhage [8] and WMHs or ALIs for cerebral ischemia [9]), whether OSA is an independent risk factor for the presence of CMBs or PVSs, and the total burden of cerebral SVD, have not yet been determined.

The objective of the present study was to investigate the association between the presence and burden of each indicator of SVD

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with the apnea–hypopnea index (AHI), which represents the severity of sleep apnea, in patients with OSA.

2. Materials and methods

2.1. Subjects

A total of 185 patients were identified who were referred to the Sleep Center of the Ewha Medical Center for suspected OSA between March 2009 and July 2014. All patients included in the study had one or more OSA-related symptom, such as: witnessed loud snoring between apneas, witnessed episodes of gasping for air, choking, sleep fragmentation/insomnia, and non-refreshing sleep [10]. Patients underwent overnight polysomnography (PSG) and brain MRI within 60 days before ($n = 160$) or after ($n = 25$) PSG. Thirteen patients were excluded who had no available gradient recalled echo (GRE) images, and two patients were excluded due to poor image quality. Therefore, a total of 170 patients were included in this study.

The main indications for performing brain MRI were: headache and dizziness ($n = 67$, 39.4%); rapid eye movement (REM) sleep behavior disorder ($n = 22$, 12.9%); patient's request ($n = 17$, 10.0%); complaints of cognitive decline ($n = 15$, 8.8%); insomnia with sleep fragmentation ($n = 13$, 7.6%); loss of consciousness history ($n = 10$, 5.9%); stroke or transient ischemic attack ($n = 9$, 5.3%); suspected restless leg syndrome or periodic limb movement ($n = 9$, 5.3%); excessive daytime sleepiness ($n = 6$, 3.5%); and narcolepsy ($n = 2$, 1.2%). All of the PSG and MRI data from the included patients were acquired before the initiation of OSA treatments (including continuous positive airway pressure therapy, CPAP).

The hospital Institutional Review Board approved the study, and the patients' informed consent was waived because of the study's retrospective and observational nature.

2.2. MRI protocol, definition of small vessel diseases and vascular stenosis

Each patient underwent a brain MRI within a median of 11 days (interquartile range: 2–41 days) from the day of PSG monitoring. The detailed protocol of the brain MRI had previously been described [11]. All MRI examinations were performed with a 3T scanner (Philips Achieva v2.6, Best, The Netherlands). Brain MRI image slices were acquired parallel to the orbitomeatal line using the following parameters: for fluid-attenuated inversion recovery (FLAIR), time repetition (TR)/time echo (TE) = 12,000/120 ms, pixel spacing = 0.449 mm/0.449 mm, field of view (FOV) = 183 × 230 mm, and slice thickness = 5 mm; for T2-weighted images, TR/TE = 15,000/90 ms, pixel spacing = 0.240 mm/0.240 mm, FOV = 176 × 220 mm, and slice thickness = 5 mm; and for GRE, TR/TE = 571/21.9 ms, pixel spacing = 0.449 mm/0.449 mm, FOV = 145 × 250 mm, and slice thickness = 5 mm [12].

The extent of white matter changes was determined on the FLAIR images for the periventricular white matter (PVWM) or deep white matter (DWM), according to Fazekas scale [13]. Fazekas scores of ≥2 in periventricular white matter hyperintensities (PVWMHs) and/or ≥2 in deep white matter hyperintensities (DWMHs) were considered to indicate high-grade white matter hyperintensities (HWMHs). An ALI was defined as a 3–15 mm lesion showing as hyperintense on axial T2-weighted images and hypointense on axial T1-weighted images in a subject lacking a relevant history of symptoms or signs [8]. The CMBs were identified as punctate hypointense lesions <10 mm in size on GRE images [14]. The PVSs were defined as punctate or linear hyperintense lesions on T2-weighted images in the basal ganglia and <3 mm in size [12]. Subjects were coded with the following grades: 0 = no PVSs, 1 ≤ 10 PVSs, 2 = 11–20 PVSs, 3 = 21–40 PVSs, and 4 ≥ 40 PVSs. High grade perivascular spaces (HPVSs) subjects were defined as those of grade 2–4, based on PVSs in the basal ganglia or centrum ovale [15] (Fig. 1). Two neurologists (TJS and JHP), who were blinded to the patients' clinical information, independently investigated the presence of HWMHs, ALIs, CMBs and HPVSs. The kappa values for the inter-observer agreement on the presence of HWMHs, ALIs, CMBs, and HPVSs were 0.89, 0.91, 0.83, and 0.84, respectively. Consensus was reached in cases of discrepancy for the detection of SVD. The total SVD (0–4) score was calculated by the summation of one point per category for the existence of CMBs, HWMHs, HPVSs, and ALIs, as outlined previously [15].

2.3. Polysomnography

Polysomnography (PSG) was performed as previously described [16]. The duration of OSA symptoms was defined as the time interval from the date of the first OSA-related symptom to the date that PSG was performed. Overnight PSG was performed with a comprehensive device (TWin® PSG Clinical Software; Grass Technologies, Warwick, RI, USA) at the sleep laboratory of the Ewha Sleep Center. Apneas were defined as events when airflow was reduced to ≥90% of the baseline values for at least 10 seconds, and apneas were further classified as obstructive type if respiratory efforts were noted on either the chest or the abdominal belt channel, or as central type if no respiratory effort was noted. Hypopneas were defined as events with a ≥ 30% reduction of airflow for at least 10 seconds and accompanied by at least a three percent drop in oxygen saturation (SaO_2) or an arousal [17,18]. The arousal index was defined as the number of arousals per hour. The AHI was calculated by averaging the total number of obstructive apneas and hypopneas per hour of sleep, and OSA severity was determined based on the AHI: no OSA (AHI < 5), mild OSA (5 ≤ AHI < 15), and moderate-to-severe OSA (AHI ≥ 15) [16].

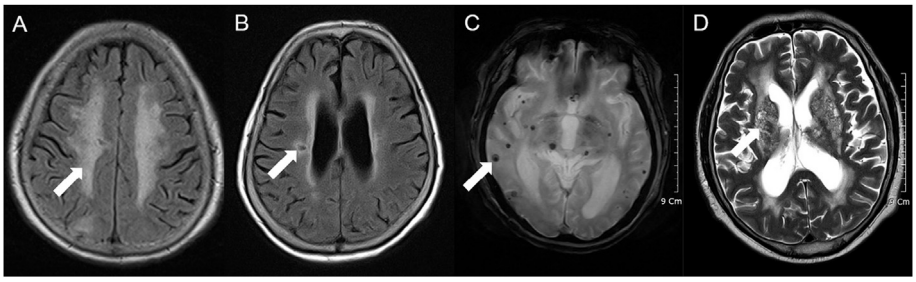

Fig. 1. (A) High-grade white matter changes (white arrowhead); (B) Asymptomatic lacunar infarction (white arrowhead); (C) Cerebral microbleeds (white arrowhead); and (D) High-grade perivascular spaces (white arrowhead).

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