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Original Article

Spontaneous improvement in both obstructive sleep apnea and cognitive impairment after stroke☆

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ABSTRACT

Background: Knowledge available about the relationship between obstructive sleep apnea (OSA) and cognitive impairment after stroke is limited. The evolution of OSA and cognitive performance after stroke is not sufficiently described.
Methods: We prospectively enrolled and examined acute stroke patients without previously diagnosed OSA. The following information was collected: (1) demographics, (2) sleep cardio-respiratory polygraphy (PG) at 72 h, day seven, month three, and month 12 after stroke, (3) post-stroke functional disability tests at entry and at months three and 12, and (4) cognition (attention and orientation, memory, verbal fluency, language, and visual-spatial abilities) using the revised Addenbrooke's Cognitive Examination (ACE-R) at months three and 12.
Results: Of 68 patients completing the study, OSA was diagnosed in 42 (61.8%) patients. The mean apnea/hypopnea index (AHI) at study entry of 21.0 ± 13.7 spontaneously declined to 11.6 ± 11.2 at month 12 in the OSA group ($p < 0.0005$). The total ACE-R score was significantly reduced at months three ($p = 0.005$) and 12 ($p = 0.004$) in the OSA group. Poorer performance on the subtests of memory at months 3 ($p = 0.039$) and 12 ($p = 0.040$) and verbal fluency at months 3 ($p < 0.005$) and 12 ($p < 0.005$) were observed in the OSA group compared to non-OSA group. Visual-spatial abilities in both the OSA ($p = 0.001$) and non-OSA ($p = 0.046$) groups and the total ACE-R score in the OSA ($p = 0.005$) and non-OSA ($p = 0.002$) groups improved.
Conclusions: A high prevalence of OSA and cognitive decline were present in patients after an acute stroke. Spontaneous improvements in both OSA and cognitive impairment were observed.

1. Introduction

Obstructive sleep apnea (OSA) as a type of sleep-related breathing disorder (SDB), is defined as interrupted breathing during sleep due to obstruction of the upper airways, with an ongoing respiratory effort. The apnea/hypopnea index (AHI) is used to grade OSA based on the mean number of apneas and hypopneas per hour of sleep [1,2]. Hypoxia and reoxygenation, hypercapnia, arousal from sleep, sleep deprivation, and negative intrathoracic pressure in patients with OSA can lead to a pathological cascade, which includes oxidative stress, inflammation, sympathetic activation, hypercoagulation, endothelial dysfunction, and metabolic dysregulation. These are linked to cerebrovascular disease and other cardiovascular diseases [2]. OSA is an independent risk factor for stroke. Stroke can aggravate or cause SDB "de novo" [3]. There are

Abbreviations: ACE-R, Revised Addenbrooke's Cognitive Examination; AHI, apnea/hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; CT, computed tomography; IC/EC, inclusion/exclusion criteria; ICU, intensive care unit; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PG, polygraphy; SDB, sleep-related breathing disorder.

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limited studies describing sleep apnea evolution after stroke. Preferential improvement of central apneas has been described [4]. It has been hypothesized that brain damage, supine position, lung or chest function worsening and acute-stroke-associated complications have negative impact on SDB pattern, but to identify the nature and cause of SDB remain unclear [3]. The association between OSA, age, stroke, and neurocognitive impairment is widely discussed. After stroke, patients with OSA perform worse on tests of attention, executive functioning, and visuoperception and psychomotor ability than those without OSA; however, age and body mass index (BMI) may also affect the results of these tests [5]. The exact prevalence of cognitive dysfunction in adult patients with OSA is unknown, but it is estimated to be at least 25% [6]. Currently available data on neurocognitive decline in patients with OSA are limited [7,8]. There is a low accessibility of polysomnography in the acute phase after stroke and low adherence to the recommended first choice therapy for OSA (continuous positive airway pressure, CPAP) [3]. This led us to hypothesize that after-stroke patients have more noteworthy cognitive impairment when they also have untreated OSA than those without OSA, that AHI has a tendency to spontaneously improve at the 12-month follow-up after stroke (ie, the level of AHI is highest just after stroke), and improvements in cognitive impairment after stroke parallel the improvement in AHI.

2. Materials and methods

2.1. Design and procedure

The aim of this prospective study was to (1) focus on previously identified risk factors for stroke and OSA coincidence in a patient based on demographic data and medical history, (2) evaluate the incidence of OSA and its evolution in stroke patients for up to 72 h after the stroke and at day seven, month three, and the 12-month follow-up, (3) examine the cognitive impairment based on the total revised Addenbrooke's Cognitive Examination (ACE-R) score, determine the decline in each subtest score of the ACE-R, and follow the evolution of the total ACE-R and its subtests at visits on months three and 12 after stroke.

Adult stroke patients who had been admitted to the stroke intensive care unit (ICU) of the department of neurology at a tertiary hospital between Monday and Friday from 2010 to 2013 were invited to participate and entered the study up to 72 h after stroke (study entry point). Patients were required to meet the protocol-specified inclusion/exclusion criteria (Table 1) and be able to provide written informed consent. The protocol was approved by the Local Ethics Committee. At admission, the National Institutes of Health Stroke Scale (NIHSS) [9,10] functional status was evaluated. Acute laboratory tests, blood pressure, heart rate, 12-lead electrocardiogram, chest X-ray, and blood oxygenation were assessed. Computed tomography (CT) with CT angiography confirmed either ischemic or parenchymal hemorrhagic stroke and excluded other brain lesion etiology. The patients underwent acute therapy based on approved European Stroke Organization guidelines [11], namely, recombinant tissue plasminogen activator was intravenously administrated, endovascular revascularization, or a combination of both. Symptomatic therapy was administered to patients who arrived late for acute therapy (ie, patients with transient ischemic attack, minor stroke, early spontaneous recovery) and in patients with cerebral hemorrhage without acute surgical intervention. Consent and initial data (checking IC/EC criteria and collecting demographic data, weight and height, and medical history of treated arterial hypertension, atrial fibrillation, ischemic heart disease including heart attack, diabetes mellitus, hyperlipidemia, previous stroke without residual neurological deficit and relevant ventilation history of snoring and clinical apneas before stroke, if known) were collected at study entry by the same physician. The degree of disability and dependence in daily activities after the stroke were measured with the NIHSS and modified Rankin Scale (mRS) [12,13] at study entry and at months three and 12, and with the Barthel Index [14] at months three and 12. Data from cardiorespiratory polygraphy (PG, Somnocheck, Weinnmann, Germany) were obtained from nasal pressure cannula (airflow recordings and snoring), respiratory effort was assessed from thoracic and abdominal wall motion sensors, and oxygen saturation and heart rate were determined from finger pulse oximetry.

Polygraphic records were visually evaluated. Apnea was defined as a reduction in airflow $\geq$90% for at least 10 s and hypopnea as reduction of airflow $\geq$50% for at least 10 s followed by oxygen desaturation $\geq$4% from baseline [5,15]. The obstructive type of apnea was defined as ongoing thoracic and abdominal effort, central apnea by no thoracic and abdominal movement, and mixed apnea as a combination of both patterns. AHI was defined as the mean number of apneas and hypopneas per hour during observed sleep. Oxygen desaturation index (ODI) was calculated as the mean number of saturation drops $\geq$4% from baseline per hour of observed sleep. OSA was diagnosed if at least 50% of respiratory events

Table 1
Study inclusion and exclusion criteria of stroke patients.

Inclusion criteria	Exclusion criteria
Ability to provide written informed consent and willingness to follow the protocol for 12 months	Quadriplegia, delirium, global aphasia, visual or hearing loss, coma
Age $\geq$18 years	Age <18 years
NIHSS $\geq$1 at admission, previous stroke with NIHSS = 0, mRS = 0, and Barthel Index = 100 points	Previous stroke with NIHSS >0, disability after previous stroke in mRS >0 and Barthel Index <100, stroke reoccurrence after study entry
Acute stroke treatment with no next planned invasive prevention procedure within one year after having had a stroke	Planned invasive secondary preventive stroke treatment (stenting, endarterectomy) or other surgery within one year after having had a stroke
CT + CTA brain scans confirming stroke of ischemic or hemorrhagic origin	Progressive or other severe central neurological condition (such as brain tumor, multiple sclerosis, epilepsy, brain edema, subarachnoid hemorrhage, brain vein thrombosis, infection of the central nervous system), severe sleep disturbances other than sleep apnea
Spontaneous ventilation	Artificial ventilation, hypoxemia caused by other medical condition (acute or chronic heart or lung failure), previous continual oxygen support (home oxygen therapy), neuromuscular disorders, previous CPAP treatment, CPAP treatment within this study, Cheyne-Stokes ventilation pattern
No previous cognitive impairment	Previously diagnosed cognitive impairment or dementia
Mood disturbances, if present, on stable dose of medication at least 3 months before stroke	Important mood disturbances if not stabilized in previous 3 months before stroke, with or without medication, or suicide in medical history
No progressive or life-threatening condition in recent medical history	Progressive or life-threatening condition (cancer, if not in remission; acute or chronic liver or kidney failure, drug or alcohol dependence)
	Pregnancy