OSAS-Related Cognitive Impairment after First-Ever Stroke: Study Design and Methodology

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Abstract: *Introduction:* Obstructive Sleep Apnea Syndrome (OSAS) is considered an emerging risk factor for cerebrovascular disease. Both the two conditions could share the same neurocognitive impairment, which, in the early phase of OSAS, are reversible and mediated by the excessive daytime sleepiness. Treatment with continuous positive air pressure (CPAP) device could improve the neurocognitive functions, and therefore, it could be considered as a valid treatment option in stroke patients affected by OSAS and neurocognitive impairment.

Materials and Methods: Patients affected by unilateral ischemic stroke will be subdivided into two groups, according to the presence or absence of OSAS. All participants will be evaluated by using a specific neuropsychological battery exploring attention, memory, praxic abilities and executive functions. Patients presented with a moderate to severe OSAS will be treated with CPAP and followed for at least 1 year.

Results: The data analysis requires a sample size of 550 to provide adequate power of the study. The outcome variable is the score of specific neuropsychological and quality of life tests at baseline, after 6 months and at 1 year follow-up.

Discussion and Conclusion: This study design presents three specific analysis limitations. First, several other sleep disorders can produce drowsiness beyond OSAS. Second, the neurocognitive impairment in stroke patients is difficult to assess. Third, OSAS patients are often intolerant to diagnostic tests requiring an excessive length.

However, the findings coming from the protocol may have important implications about the effect of sleep disorders on cognitive function in stroke patients. Moreover, the easy employed procedures could be translated into clinical practice to improve the quality of life of patients affected by both OSAS and stroke.

Keywords: OSAS, neurocognitive impairment, stroke, CPAP.

1. INTRODUCTION

Recent studies have demonstrated how Obstructive Sleep Apnea Syndrome (OSAS) and stroke share common risk factors. A direct association between the two conditions has been widely evaluated considering OSAS as another risk factor for cerebrovascular events [1].

OSAS is a common disorder characterized by repetitive pharyngeal collapses during sleep, leading to a reduction or a cessation of the airflow. During the physiological REM-sleep muscle atonia, anatomical variant of the pharynx (i.e. hypertrophic palatal soft tissue) and increased fat deposition tend to promote the obstruction through a reduced reflex-driven activation of pharyngeal dilator muscles [2-7]. To restore the normal pharyngeal patency, individuals may present frequent arousals from sleep due to the activation of sympathetic nervous system, causing a high fragmentation of sleep, and leading to low efficient sleep and excessive daytime sleepiness (EDS) [8].

Recently, OSAS is receiving increased attention because its high social-health and economic burden, mainly related to its neurocognitive and cardiovascular consequences that determine high hospitalization rate, increased road and domestic accidents, and eventually patient's death [9-10].

Both neurocognitive and cardiovascular consequences in patients with OSAS are related to the chronic sympathetic hyperactivation, leading to a diffuse vasoconstriction and systemic hypertension [11].

The main cognitive dysfunctions of severe OSAS are related to the important drowsiness, determining a loss of interest and a reduced productivity [12]. Chronically, OSAS patients can also present attention and short memory deficits, depressive mood and loss of executive function. These deficits are reversible and mainly mediated by the EDS at the beginning of the disease.

The repeated exposure to hypoxia and the typical cerebral hemodynamic perturbation due to the sympathetic activity could lead to a structural change in the brain with a more stable cognitive deficit in the

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advanced phase of OSAS [13-15]. The loss of executive function and manual dexterity seems to be more associated with the latter condition rather than to the EDS, because they persist after adequate therapy for OSAS [16-19].

An increasing prevalence of Sleep-related Breath Disorders (SDB) has been found in 40-70% of patients affected by Transient Ischemic Attack (TIA) or stroke. OSAS seems to be a condition preceeding cerebrovascular disease, although its presence may worsen the general outcome of stroke patients [20-22].

Neurocognitive impairment may be showed in the acute phase of stroke as well as in OSAS patients. The "cognitive stroke syndrome" presents different clinical features in relation to the brain region involved. The OSAS patients and those affected by thalamic and diencephalic stroke share the same neuropsychological dysfunctions such as memory, attention, visuo-spatial abilities, praxic-constructive and planning abilities [23]. A complete management of the altered neuropsychological function should be assessed in stroke patients during chronic phase to improve their quality of life. To our knowledge, there is no clinical evidence concerning the correlation between neurocognitive impairment and OSAS after 6 months of a cerebrovascular event onset. Neurocognitive dysfunction in OSAS is reversible when therapy is applicable. The treatment of choice of OSAS is based on the application of a nocturnal nasal continuous positive airways pressure (CPAP) device. Indeed, a long-term CPAP therapy can resolve pharyngeal obstruction improving blood pressure profile, sleep efficiency and EDS. However, OSAS patients with stroke showed a lower compliance to CPAP (less than 20%), that is mostly related to disability rank, low acceptance of device, and presence of language disorders (aphasia) or depressive mood [24-27].

The presented protocol is designed to test the influence of OSAS on the onset and progression of neurocognitive impairment in patients affected by a first-ever stroke.

To achieve this goal, this study is aimed at comparing the clinical features of stroke patients affected by OSAS with those without OSAS. The primary endpoint is to determine whether the presence of OSAS worsen the neurocognitive functions. The evaluation of CPAP compliance and its correlation with clinical stabilization, quality of life and psychological assessment will be considered the secondary endpoint.

2. MATERIALS AND METHODS

This protocol is designed as a pilot randomized clinical trial with two phases. In the first phase, patients referring to our cerebro-vascular out-patients' unit, affected by first ever supratentorial unilateral stroke, and presenting with a neurocognitive impairment will be screened for sleep disorders. Patients will be subdivided into two groups, according to the presence or not of OSAS. All the patients affected by severe OSAS will be treated with CPAP device, and assessed after 6 months and 1 year of therapy.

2.1. Eligibility and Exclusion Criteria

Outpatients affected by unilateral supratentorial ischemic stroke in the chronic phase (with an age range 18 - 80 years), suffering from neurocognitive disorders, will be enrolled in the study. All the patients will undergo an accurate medical history to evaluate stroke onset, vascular risk factor and habits. Then, they will be evaluated regarding quality of life, quality of sleep, mental state, anxiety and depressive symptoms through Mini Mental State Examination (MMSE), Epworth Sleepiness Scale (EES), Beck Depressive Inventory (BDI), Hamilton Anxiety Rating Scale (HARS), Pittsburg Sleep Quality Index (PSQI), Questionnaire of Quality of Life Short Form 36-item 2nd version (SF36-2v).

Patients presenting with moderate to severe cognitive impairment (MMSE < 20) or depressive symptoms (BDI > 18), as well as those affected by a severe Chronic Obstructive Pulmonary Disease with a FEV_1 < 50%, will be excluded from the study. The use of drugs such as benzodiazepine, antipsychotics, antidepressants and dopaminergic agents will be considered an exclusion criterion, as they could modulate the pontine respiratory centre activity.

The presence of mild to moderate leukoaraiosis did not exclude the patients from the study.

2.2. Phase I: Clinical Assessment

All the patients will undergo an accurate general and neurological examination. Habits, personal history and predisposing condition to cerebrovascular events will be screened to detect main vascular risk factors. CT scan and/or MRI will be performed to classify the patients into 4 categories, according to Bamford's Criteria, i.e. lacunar syndromes (LACS), posterior circulating syndromes (POCS), total anterior circulating syndromes (TACS) and partial anterior circulating syndromes (PACS) [28].

Table 1: The Neuropsychological Tests Used to Asses Post-Stroke Patients with OSAS

A. Executive Functions and Attention

- ✓ *Simple Reaction Time Task (permanent attention and vigilance):* In simple reaction time experiments, there is only one stimulus and one response. The subject will be required to press the space bar every time a stimulus (i.e. a coloured star) will appear on the screen. The reaction time, that is the time required for a subject to respond to the presence of a stimulus, will be measured.
- ✓ *Trial Making Test A and B (selective and divided attention):* The subject will be showed some numbers distributed over a sheet of paper. The subject will be required to join all numbers with a pen in sequential way as quickly as possible (step A). Then, the subject will be showed another sheet of paper with numbers and letters. This time, the subject will be required to join numbers and letters as quickly as possible alternating a number with a letter and following the numeric and alphabetic order (step B).
- ✓ *Wisconsin Card Sorting Test (planning ability):* The subject will be presented four cards, the so called "guide cards" representing different drawings, a red triangular, two green stars, three yellow crosses and four blue circles. Then, the subject will receive other cards representing the same drawings arranging in a different way. The subject will be asked to associate each card to the "guide cards" according to a logical criterion (ex: colour, shape, number) previously established by the examiner. The criterion will be changed after ten right consecutive responses and the subject will have to identify every time the right criterion.

B. Short and long term verbal memory and verbal learning

- ✓ *Rey Auditory Verbal Learning Test:* The standard Rey Auditory Verbal Learning Test format starts with a list of 15 words, which an examiner reads aloud at the rate of one word for second. The patient will have to repeat in any order all the words able to remember. This procedure will be administered for a total of five times.

  After about 15 minutes, the patient will be required to say all the previous words able to retrieve.
- ✓ *Digit span test (forward and backward):* The examiner will say to the subject some progressively more complex sequences of numbers. After each sequence the subject will have immediately to repeat numbers in the same order (forward). The short-term verbal memory span corresponds to the maximum length of the sequence of numbers that the subject is able to repeat without errors (the test will finished when the subject will fail two consecutive sequences of numbers).

  After this test, the examiner will say again to the subject some progressively more complex sequences of numbers, but this time, after each sequence the subject will have to repeat numbers in the opposite order, from the last number to the first one (backward). Through this task the working memory will be evaluated.

C. Praxic-constructive abilities

- ✓ *Rey-Osterrieth Complex figure (copy):* The examiner will show to the subject a drawing, the so called "Rey figure". The subject will be required to copy the drawing without time limits.

D. Short and long term visuospatial memory

- ✓ *Rey-Osterrieth Complex figure (immediate and delayed recall):* The examiner will ask to the subject to remember the previously copied drawing and to reproduce it on a blank sheet of paper (immediate recall). The subject will be required the same task after about 15 minutes from the first recall (delayed recall).

Then, the patients will be investigated by means of specific a neuropsychological diagnostic tool shown in Table **1**. The cognitive domains affected by the diseases are attention, memory (verbal and visuo-spatial), praxic abilities and executive functions like planning ability [29-36].

Finally, all the enrolled patients will undergo a home-monitoring polysomnography (PSG) to detect the presence of respiratory events during the night, according to the Chicago criteria for apnea or hypopnea. A sleep medicine skilled neurologist will determine the Apnea-Hypopnea Index (AHI) defined as the number of apnea or hyponea per hour of sleep. The AHI will group the OSAS patients into 3 categories, according to the presence of mild (AHI range 5-15) moderate (AHI range 15-30) and severe disease (AHI > 30). Patients affected by moderate to severe OSAS will be treated by using a CPAP setting after a titrating night [37]. If the patient refuses the CPAP therapy, he/she will be excluded from the study.

2.3. Phase II: Follow-Up

Aim of this phase is the evaluation of CPAP compliance, and eventually the improvement of psychological function. At follow-up, patients will be clinically evaluated to detect the frequency and the correct use of the CPAP device. A good OSAS outcome is determined with a daily use of CPAP for at least 4 hour per night. Clinical outcome will be detected both through an interview to score EDS and the sleep quality by using ESS, PSQI and SF-36. The improvement of specific neuropsychological functions (i.e. attention, memory and executive function) will be screened by means of the same neuropsychological battery of Phase I.

The first visit will be performed 6 months after the beginning of CPAP therapy. All the study participants will be followed for at least 1 year.

2.4. Outcomes

The outcome measures of this study are specific neuropsychological tests and quality of life scores.

In the randomization phase data will be collected from a population of consecutive outpatients presented with neurocognitive impairment during the chronic phase (i.e. at leat 6 months after the cerebrovascular event). Data will include: type of cerebrovascular event

(LACS, TACS, PACS, POCS), presence or not of diabetes mellitus, hypertension and hypercholesterolemia, MMSE, PSQI, SF36-2v, ESS, BDI, HARS, specific neuropsychological outcomes (see Table **1**) and AHI scores, and acceptance or not of CPAP device.

The follow-up data (i.e. at 6 and 12 months after the enrollment) will include CPAP compliance (length per night, night per week), PSQI, SF36-2v, ESS and specific neuropsychological testing scores.

2.5. Data Analysis

The data analysis requires a correct sample size to provide adequate power for the study comparison and to reduce Type I (α) and Type II (β) error impact. A sample of 550 cases is designed to be the minimum size considering a normal distribution of OSAS, the prevalence of OSAS in patient with cerebrovascular events, the degree of acceptance and compliance of CPAP [19,24,27,38]. The interval confidence is set to 95%.

The primary endpoint is to evaluate the impact of OSAS on the neurocognitive impairment in stroke patients during chronic phase. The primary null hypothesis was: patients affected by first-ever stroke and OSAS present the same degree of neurocognitive impairment of those stroke patients without OSAS. Alternative hypothesis is: the neurocognitive impairment in OSAS patients after first-ever stroke is higher than in those without OSAS.

The second endpoint will be the evaluation of CPAP compliance. The null hypothesis was: the presence of neurocognitive impairment does not modify CPAP compliance. Alternative hypothesis was: the neurocognitive impairment worsens CPAP compliance.

The third endpoint was to determine the correlation between neurocognitive impairment and degree of OSAS with the following null hypothesis: neurocognitive impairment and quality of life are the same of the baseline after 6 months and 1 year of CPAP treatment. Alternative hypothesis was: will the neurocognitive impairment and quality of life improve after CPAP treatment?

The three null hypotheses should be tested with t-student tool for paired data with a confidence interval set to 95%.

3. DISCUSSION

This study protocol is designed as a randomized clinical trial with easy employed interventions and procedures. The results of this trial might have important implications in translating the proposed interventions into clinical practice. Indeed, this study protocol will generate important and novel information about the effect of sleep disorders on cognitive function in stroke patients, leading to a possible improvement of their quality of life.

However, this protocol presents some analysis limitations.

First, EDS is caused not only by OSAS but also by other sleep disorders such as insomnia with low sleep efficiency. Thus, this study might also be extended to all the sleep disorders which could cause EDS. Second, the causes of neurocognitive impairment in patients presented with stroke are wide and difficult to assess. Moreover, the relationship between stroke and OSAS is still poor understood. To the best of our knowledge, only cross-sectional analyses have pointed out a high prevalence of SBD in patients after cerebrovascular events. In 2005, Yaggi at al. performed the largest case-control study highlighting the prevalence of stroke and death in patients presented with OSAS, showing that OSAS could represent an independent vascular risk factor [1]. However, this association has to be comfirmed by other epidemiological studies.

Third, the length of specific neuropsychological test is set at around 1 hour. OSAS patients are often irritable and intolerant to diagnostic tests. Although this overburden period is necessary to explore all the specific cognitive functions, we expect that patients will not complete their work since they usually have scarce compliance to all those diagnostic procedures with an excessive duration time.

CONCLUSIONS

This study design is aimed to evaluate and assess the impact of EDS in the genesis of cognitive impairment in patients affected by first-ever stroke. Given that OSAS is considered an overall risk factor for stroke and that sometimes OSAS is clinically evident only after the stroke onset, the cognitive syndromes in patients following stroke could improve after CPAP treatment due to EDS improvement.

CONFLICT OF INTEREST

The authors state neither conflict of interest nor financial support.

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