Sleep-Disordered Breathing in the Acute Phase after Stroke and Neuropsychiatric Outcomes

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Background/Objectives

Stroke is the second leading cause of death and a common cause of acquired disability worldwide, and the burden of the disease at the societal level is expected to increase in the coming decades (1-4). Stroke can result in various long-term consequences, both neurological (such as aphasia, paresis, sensory or visual disturbances, and coordination and balance disorders) and neuropsychiatric (such as cognitive impairment, depression, and fatigue) (5-8). These consequences, in turn, affect stroke survivors' physical functions, activity levels, and ability to participate in daily activities (9-13).

Post-stroke fatigue is common, with prevalence estimates ranging between 25- 85%, and 40% of stroke survivors have reported it as one of their worst symptoms (14-16). Recent Swedish studies have estimated the long-term prevalence 3-5 years after stroke to be between 24-52% (17, 18). Post-stroke fatigue partially overlaps with post-stroke depression, but approximately 70% of individuals with significant fatigue do not exhibit concurrent depressive symptoms (17). The condition is associated with poorer performance in daily activities and lower health-related quality of life (17). Currently, there are no specific treatments for post-stroke fatigue (19). Due to its high prevalence and consequences, it has recently been identified as one of the top ten priority research questions in stroke rehabilitation by the UK National Institute for Health and Care Research (20).

There are conflicting reports on whether traditional vascular risk factors such as hypertension, hyperlipidemia, heart disease (including atrial fibrillation), and smoking contribute to post-stroke fatigue (21, 22). Obesity is associated with post-stroke fatigue, and sleep-disordered breathing (SDB) has also emerged as a potential risk factor (23).

Sleep-disordered breathing is prevalent after stroke, occurring in 50-70% of some populations (25). The dominant condition is obstructive sleep apnea syndrome (OSAS), followed by central sleep apnea (26). Established treatments for OSAS include continuous positive airway pressure (CPAP), mandibular advancement devices, surgical interventions, and weight loss (26), which can reduce daytime sleepiness. Research is ongoing regarding the extent to which treated OSAS can contribute to secondary prevention in stroke (27). Current American guidelines for secondary prevention provide a class 2b recommendation with moderate evidence for considering OSAS screening after stroke or transient ischemic attack (TIA) (28). The diagnosis is primarily made through overnight respiratory monitoring, with polysomnography being the gold standard, although it is time- and resource-intensive and may be cumbersome for the patient (29). Limited polygraphic examinations can also be conducted both in hospitals and at home (29).

Research Questions:

1. What is the 1-year prevalence of post-stroke fatigue in a hospital-based cohort in Blekinge?
2. How many individuals with stroke have significant sleep-disordered breathing according to non-invasive measurement?
3. What proportion of individuals with post-stroke fatigue had significant sleep-disordered breathing during hospitalization?
4. Can early, non-invasive, and simple measurement of sleep-disordered breathing in hospitals predict a subgroup of stroke patients who will develop significant fatigue?
5. Is there evidence that treatment goals after stroke are achieved to a lesser extent in those with significant fatigue?

By answering these questions, our study aims to: i) Facilitate patient selection for potential future clinical trials, e.g., CPAP treatment for preventing/treating post-stroke fatigue. ii) Identify potential subgroups among individuals with post-stroke fatigue. iii) Investigate risk factors for post-stroke fatigue, including sleep-disordered breathing. iv) Examine whether fatigue leads to poorer adherence to secondary preventive treatment goals (30).

Methodology

The present study has been approved by the Swedish Ethical Review Authority, diary number 2024-02659-01.

Study participants will be prospectively identified at the Department of Medicine, Blekinge Hospital, Karlskrona. Inclusion and exclusion criteria are as follows:

Inclusion criteria:

- Age >18 years
- Stroke according to WHO definition (31) (ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage)
- TIA with MRI-verified lesions corresponding to symptoms
- Informed consent to participate

Exclusion criteria:

- Traumatic stroke
- Tumor-associated bleeding
- Expected survival <3 months
- Unconsciousness (RLS >3)

Potential participants will be identified by medical staff, and informed consent will be obtained by a researcher.

Upon obtaining consent, patients will be equipped with a Withings Sleep Analyzer and a Nonin WristPro 2 pulse oximeter during hospital stay days 1- 3.Withings Sleep Analyzer is validated to detect moderate-severe obstructive sleep apnea (32). The patient is also equipped with a Nonin WristPro 2 pulse oximeter with the possibility to retrospectively obtain registered data regarding nocturnal hypoxia (T90 – time under 90% oxygen saturation, and ODI – oxygen desaturation index).
Baseline data collected include:

- National Institutes of Health Stroke Scale (NIHSS) (33)
- Pre-stroke modified Rankin Scale (mRS) (34)
- Previous stroke history
- BMI
- STOP-BANG questionnaire (35)

If it is not possible to obtain these data, including NIHSS, during the hospital stay, they will be collected later through chart review when possible. During chart review/clinical examination, the following will also be recorded:

- Main subtype of stroke (IS, ICH, SAH)
- Oxfordshire Community Stroke Project classification (OCSP) (36)
- Trial of Org 10172 in acute stroke treatment (TOAST) classification (37)
- Charlson Comorbidity Index (CCI) (38)
- Hypertension (>140/90 mmHg at discharge or antihypertensive treatment in the last 2 weeks)
- Diabetes mellitus (previous diagnosis, fasting blood glucose >6.1 mmol/L, or non-fasting blood glucose >11 mmol/L)
- Heart disease (ischemic heart disease, previous MI, angina, PCI, CABG, heart failure, arrhythmias)
- Hyperlipidemia (previous diagnosis, lipid-lowering treatment, total cholesterol >5 mmol/L, LDL >3 mmol/L)
- Smoking
- COPD (ICD-10 J44 or described in chart)
- Depression diagnosis (ICD F32-33) or antidepressant treatment
- HbA1c, lipid status, blood pressure at discharge
- Medications (antiplatelets, anticoagulants, antidiabetics, antihypertensives, opioids, sedatives, statins, antidepressants) at onset and discharge
- Long-term ECG monitoring
- Carotid stenosis degree on carotid ultrasound exam
- Coagulation assessment, if performed
- Previous stroke/recurrent stroke within 1 year

Participants are subsequently invited via letter for a follow-up visit approximately 1 year after stroke (+3 months, but not earlier than 1 year) at the district nurse students' training clinic at Blekinge Institute of Technology. During this visit, the following will be recorded:
Follow-up assessment (1 year after stroke):

- Fatigue Assessment Scale (FAS) (39)
- Fatigue Visual Analogue Scale (VAFS)
- PHQ-9 depression scale (40)
- mRS (34)
- Blood pressure
- Height, weight, BMI
- Blood tests (HbA1c, lipid profile)
- Smoking
- Medication adherence
- Stroke Impact Scale (41)
- Ongoing BiPAP or CPAP treatment
- Alcohol consumption

Recruitment Calculation
With a confidence level of 0.05, statistical power of 80%, an estimated OSAS prevalence of 50%, and estimated significant fatigue prevalence of 30%, a total cohort of 284 participants is required to detect a doubled relative risk of significant fatigue with OSA. Considering a 10-20% loss to follow-up, approximately 340 participants need to be included.

Ethical Considerations
The project involves non-invasive procedures except for blood sampling at follow-up. Written informed consent will be obtained.
Data for research purposes such as apnea-hypopnea index and time under 90% blood oxygen saturation are collected outside of clinical praxis and do not in any way hinder concurrent investigation for OSA if clinically indicated. The sleep study data will be interpreted at the 1-year follow-up and the study physicians will decide if further investigation is needed.

Affiliated Researchers
Researcher Joseph Aked is the principal investigator, with Anders Behrens and Arne Lindgren as co-investigators.

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