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Original Article

Clinical phenotypes of obstructive sleep apnea after ischemic stroke: a cluster analysis

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is highly prevalent in patients with ischemic stroke. Untreated OSA is associated with an increased risk of cardiovascular morbidity and OSA treatment may improve neurological recovery in stroke survivors, yet OSA in stroke patients remains poorly characterized. The goal of this study is to identify clinical phenotypes of ischemic stroke patients with OSA.
Methods: Participants (n = 451) with ischemic strokes and OSA (respiratory-event-index, (REI) ≥ 10/hour based on home sleep apnea testing) were identified from the Brain Attack Surveillance in Corpus Christi (BASIC) project. Latent class analysis was performed based on the following variables: age, sex, race/ethnicity, REI, pre-stroke snoring, pre-stroke tiredness/fatigue, pre-stroke sleep duration, prior stroke history, NIHSS at presentation, body mass index (BMI), hypertension, diabetes, atrial fibrillation, coronary artery disease, and chronic heart failure.
Results: A model with three phenotype clusters provided the best fit. Cluster 1 (n = 55, 12%) was defined by higher NIHSS scores. Participants in cluster 2 (n = 253, 56%) were younger and had relatively low NIHSS scores. Cluster 3 (n = 143, 32%) included participants with severe OSA and higher prevalence of medical comorbidities.
Conclusion: Ischemic stroke survivors with OSA can be categorized into three clinical phenotype clusters characterized by differences in stroke severity, OSA severity, age and medical comorbidities. This highlights the heterogeneity of post-stroke OSA. Awareness of the different faces of OSA in patients with ischemic stroke may help clinicians identify OSA in their patients, and inform research concerning the pathophysiology, treatment and prognostic impact of post-stroke OSA.

1. Introduction

Obstructive sleep apnea (OSA) is associated with an increased risk for incident stroke [3], and OSA severity predicts functional outcomes after ischemic stroke [2]. OSA is highly prevalent in stroke patients, affecting up to 70% of all stroke survivors [1]. Despite the high prevalence of OSA, only a minority of stroke patients undergoes testing and, if indicated, treatment for OSA [4], perhaps because no definitive trial has shown treatment benefit in this population.

Recent efforts have aimed at better characterization of the different clinical phenotypes of OSA in the general non-stroke population. Several cohort studies investigating symptom clusters suggest three distinct clinical presentations of OSA: first, patients who present with disturbed sleep or insomnia; second, patients whose chief complaint is excessive sleepiness; and third, minimally symptomatic patients [5–7]. Additional subtypes vary between studies.

Abbreviations: BASIC, Brain Attack Surveillance in Corpus Christi; BMI, Body Mass Index; CAD, Coronary Artery Disease; CHF, Chronic Heart Failure; NIHSS, National Institute of Health Stroke Scale; REI, Respiratory Event Index; OSA, Obstructive Sleep Apnea.

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Of note, these clinical phenotypes were based on samples of participants from the general population or patient populations referred for sleep testing. However, post-stroke OSA patients tend to have fewer OSA symptoms, and contain a higher proportion of females affected, compared to the general OSA population. Therefore, it is unclear whether the above phenotypic clusters apply to post-stroke OSA patients. The aim of this study is to better understand the heterogeneity of OSA in stroke survivors. The use of latent class analysis allows for identification of symptom clusters within this cohort of stroke survivors, without a priori assumptions regarding subgroup features. This approach of categorizing entities into homogeneous subgroups or clusters has been widely used, for example to predict treatment adherence and health outcomes in patients with hypertension [8] or to identify to genes with similar functions [9]. Characterization of phenotypes is the initial step in identification of subgroups with different prognosis and treatment responsiveness.

2. Methods

2.1. Study population and procedure

The Brain Attack Surveillance in Corpus Christi Project is a population-based study that uses active and passive surveillance to identify all strokes in Nueces County, Texas, residents aged 45 years or older. Methods have been described previously in detail [10,11]. Briefly, ischemic stroke is based on the clinical definition of an acute onset of focal neurological deficit persisting for ≥24 h and attributable to an ischemic event following a cerebrovascular distribution. Patients on supplemental oxygen, mechanical ventilation, other positive pressure ventilation as well as pregnant patients were excluded. For this analysis, participants age, sex, race/ethnicity, height, weight, initial NIH stroke scale (NIHSS) scores, history of previous stroke/transient ischemic attack (TIA), hypertension, diabetes mellitus, coronary artery disease, chronic heart failure and atrial fibrillation were obtained from patient medical records. Home sleep apnea testing (ApneaLink Plus, ResMed Inc., San Diego, CA) was performed within 45 days of stroke onset. Nasal pressure (airflow), oxygen saturation, pulse, and respiratory effort (thorax excursion) were recorded to assess for OSA. Apneas were defined by a decrease in nasal pressure of ≥80% from baseline for ≥10 s. Hypopneas were defined by a decrease in nasal pressure of ≥30% compared to baseline, lasting ≥10 s and associated with a ≥4% oxygen desaturation. If oximetry data were missing, hypopneas were defined as a reduction in nasal pressure of ≥50% for ≥10 s. Automated scoring software was used to derive the respiratory event index (REI), defined as the sum of all apneas and hypopneas divided by hours of recording. All studies were reviewed by a registered polysomnographic technologist for artifact and inappropriately scored events [12]. OSA was defined as an REI ≥10/hour. Using this cutoff, ApneaLink has a sensitivity of 0.98 and specificity of 1.0 to identify OSA, compared to gold-standard polysomnography [13]. To assess pre-stroke symptoms of OSA, the Berlin questionnaire, which includes questions about snoring/apnea, sleepiness and hypertension was completed by either the participant or a proxy [14]. Self-reported sleep time prior to stroke was categorized into short (≤6 h), normal (7–8 h) or long (≥9 h) based on the consensus statement from the American Academy of Sleep Medicine [15]. All participants or a surrogate provided written consent to participate in this study. The University of Michigan and Corpus Christi hospital systems' Institutional Review Boards approved this project (IRB project number HUM00041536 approved through 1/21/2020).

2.2. Statistical analysis

Latent class analysis was used to identify classes based on the following variables: snoring (≤2 nights per week, ≥3 nights per week), tiredness/fatigue (≤2 nights per week, ≥3 nights per week), history of prior stroke/TIA, congestive heart failure, coronary artery disease, diabetes, hypertension, sex, race/ethnicity (Mexican-American, non-Hispanic white), atrial fibrillation, sleep duration (≤6 h, 7–8 h, ≥9 h), age, body mass index (BMI), NIHSS, and REI. Age and BMI were included as continuous variables; NIHSS and REI as Poisson/count variables. All other variables were included as categorical. Participants who had <2 h of valid sleep study data or an REI <10/hour were excluded from the analysis as inadequately assessed or unlikely to have substantial sleep apnea, respectively. Participants with missing case data or of race/ethnicities other than Mexican-American or Non-Hispanic White were also excluded from the analytical cohort. MPlus was used to run latent class analysis with two to five clusters and to choose the number of clusters based on the Vuong-Lo-Mendell-Rubin likelihood ratio test (LRT) and Lo- Mendell-Rubin adjusted LRT as well as clinical relevance. For descriptive purposes, we used the empirical Bayes modal method to assign each individual to a single class. Descriptive statistics for the classes were based on the assigned class membership.

3. Results

3.1. Cohort

The analytical cohort consisted of 451 BASIC participants. Sample characteristics are summarized in Table 1. The median number of days from stroke presentation to sleep testing was 13 days (interquartile range 6, 21).

3.2. Cluster analysis

Latent class analysis revealed that a model with three distinct clusters had the best fit. Fig. 1 illustrates the differences in age, REI and NIHSS among clusters.

3.2.1. Cluster 1: severe strokes

Cluster 1 consisted of 55 participants (12%) characterized by a rather severe neurologic deficit based on a mean NIHSS score of 15.6.

3.2.2. Cluster 2: younger patients with mild strokes and relatively mild OSA

Participants in cluster 2 (n = 253, 56%) had on average, in comparison to other clusters, younger ages with a mean age of 65.1 years, the mildest strokes with a mean NIHSS of 2.9, and less severe OSA with a mean REI of 18.5/hour.

3.2.3. Cluster 3: severe OSA with high prevalence of co-morbidities

Cluster 3 participants (n = 143, 32%) had severe OSA based on a mean REI of 45.1/hour. A higher proportion of participants in cluster 3 had coronary artery disease (41%, $p = 0.046$) compared to clusters 1 and 2. Additionally, there was a trend towards a higher proportion of participants with co-morbid diabetes mellitus (65%, $p = 0.054$) and male participants (68.5%, $p = 0.074$) compared to clusters 1 and 2.

4. Discussion

This study of 451 ischemic stroke patients with OSA reveals three phenotypic clusters, based on demographic information, stroke severity, OSA severity, and medical co-morbidities. Cluster 1,

Table 1
Clinical characteristics by phenotype cluster, based on the assigned class membership for each individual.

Participant characteristics	Overall cohort n = 451	Cluster 1 n = 55	Cluster 2 n = 253	Cluster 3 n = 143	p-value
Age	67.1 (11.5)	70.6 (12.5)	65.1 (11.1)	69.2 (11.2)	<0.001
Male gender – n (%)	276 (61.2)	34 (61.8)	144 (56.9)	98 (68.5)	0.074
Race/Ethnicity – n (%)					0.410
- Mexican American	311 (69%)	42 (76.2)	179 (67.2)	99 (69.2)	
- Non-Hispanic White	140 (31%)	13 (23.6)	84 (32.8)	44 (30.8)	
BMI	30.3 (6.5)	29.1 (5.8)	30.2 (7.0)	30.9 (5.7)	0.090
NIHSS	5.1 (5.5)	15.6 (6.7)	2.9 (2.4)	4.8 (4.1)	<0.001
REI	27.2 (14.5)	21.1 (7.4)	18.5 (5.7)	45.1 (10.6)	<0.001
Snoring (≥3 nights/week) – n (%)	235 (52.1)	33 (60.0)	126 (49.8)	76 (53.1)	0.373
Tiredness (≥3 days/week) – n (%)	146 (32.4)	15 (27.3)	81 (32.0)	50 (35.0)	0.575
Sleep duration					0.446
- ≤6 h	151 (35.7)	21 (38.2)	93 (36.8)	47 (32.9)	
- 7–8 h	207 (45.9)	20 (36.4)	116 (45.8)	71 (49.7)	
- ≥9 h	83 (18.4)	14 (25.5)	44 (17.4)	25 (17.5)	
Stroke history – n (%)	131 (29)	15 (27.3)	75 (29.6)	41 (28.7)	0.934
CHF – n (%)	33 (3.7)	1 (1.8)	20 (7.9)	12 (8.4)	0.244
CAD – n (%)	147 (32.6)	17 (30.9)	72 (28.5)	58 (40.6)	0.046
Diabetes mellitus – n (%)	256 (56.8)	29 (52.7)	134 (53.0)	93 (65.0)	0.054
Hypertension – n (%)	392 (86.9)	44 (80.0)	218 (86.2)	130 (90.9)	0.108
Atrial fibrillation – n (%)	53 (22.8)	7 (12.7)	27 (10.7)	19 (13.3)	0.719

Values are means ± standard deviation unless otherwise stated. BMI – Body Mass Index. NIHSS – National Institutes of Health Stroke Scale. REI – Respiratory Event Index. CHF – Chronic Heart Failure. CAD – Coronary Artery Disease. P-values are from one-way ANOVA tests for continuous variables, and chi-square tests for categorical variables.

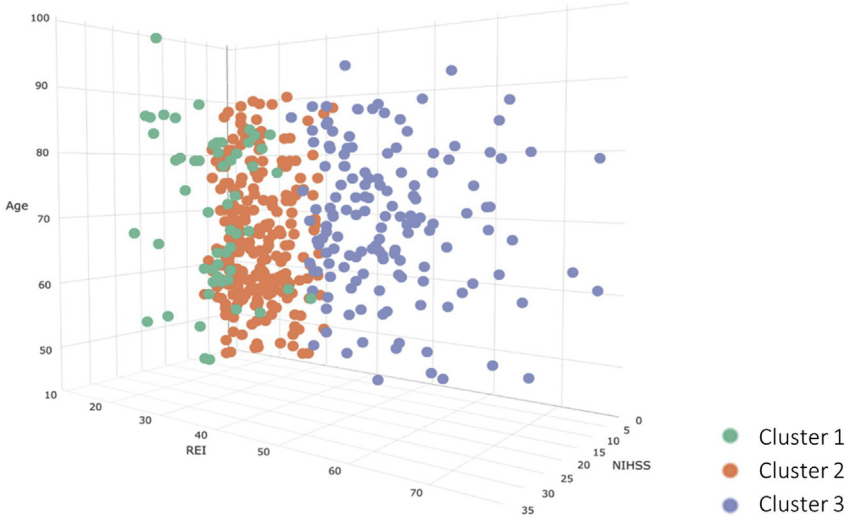

Fig. 1. Scatterplot indicating age, REI and NIHSS for each participant by cluster to highlight the differences between the groups, based on the assigned class membership for each individual.

the smallest group, contained patients with the most disabling strokes. Participants in cluster 2, the most populous group, were on average younger than those in other clusters and had milder strokes. Cluster 3 was characterized by participants with severe OSA and a high prevalence of medical co-morbidities.

Previous population-based studies of OSA phenotypes in non-stroke populations revealed subgroups of clinical phenotypes characterized by the predominant clinical complaint of disturbed sleep, excessive daytime sleepiness or minimal OSA symptoms [6,7]. In our cohort, a large proportion of participants did not report typical OSA symptoms such as snoring or daytime tiredness despite moderate-severe OSA. This observation aligns well with previously published evidence that stroke patients with OSA are less likely to endorse the typical clinical complaints of non-stroke patients with OSA [16].

One limitation of this study is that recall bias may have influenced the results of reported sleep apnea symptoms. In addition, we did not collect information about craniofacial characteristics or other sleep disorders such as insomnia, and therefore identification of a disturbed sleep/insomnia subgroup or one with particular craniofacial characteristics as seen in previous work [17,7] was not possible in this study.

The strengths of this study include a well characterized cohort of ischemic stroke survivors. OSA was diagnosed using objective data collected with a home sleep apnea test. The study population was ethnically diverse. A limitation is that home sleep apnea tests rather than gold-standard in-laboratory polysomnography was used to assess for OSA. However, the particular device used has been well validated, and it allowed characterization of a post-stroke sample that would not have been accessible for study in many cases had in-laboratory testing been required.

5. Conclusion

Ischemic stroke patients with OSA can be categorized into three different clusters, distinguished notably by stroke severity, age, OSA severity, and medical co-morbidities. Awareness of the heterogeneity of post-stroke OSA can help clinicians identify patients at risk.

These findings may also guide future research to investigate whether these clusters are differentially related to pathophysiological mechanisms and divergent clinical outcomes.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.04.004.

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