A Retrospective Comparison of Seizure-Related Characteristics in Epilepsy Patients with and without Obstructive Sleep Apnea

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Abstract

Background: Obstructive sleep apnea (OSA) is prevalent in people with epilepsy (PWE), and confers increased risk of morbidity and mortality. While evidence exists for the amelioration of seizure-related characteristics after OSA treatment with continuous positive airway pressure, limited literature exists comparing PWE and OSA to PWE without OSA. The aim of this study was to determine whether seizure-related characteristics differ between PWE and OSA and PWE without OSA.

Methods: A retrospective study of consecutive PWE ≥ 18 years of age who were referred for evaluation of suspected OSA was performed at a single academic center. Charts were individually reviewed for OSA and seizure-related characteristics. Pearson’s χ², t-testing, and binominal logistic regression was used as appropriate. A p < 0.05 was considered statistically significant.

Results: Of 159 PWE referred for PSG for suspected OSA, 100 were diagnosed with OSA. PWE and OSA were older and diabetic, and unclassified epilepsy was more common in those with moderate and severe OSA, and also associated with older age. PWE without OSA were more likely to be on monotherapy and prescribed a glutamate blocking antiepileptic drug (AED). Seizure freedom was also more common in those without OSA compared to those with moderate OSA.

Conclusions: Seizure freedom, monotherapy, and glutamate blocking AEDs are more common in PWE without OSA compared to those with OSA. A U-shaped relationship may exist between OSA severity and seizure freedom, and the diagnosis of unclassified epilepsy syndromes may be more likely in those with moderate and severe OSA due to age-related characteristics.

Keywords: Seizures; Epilepsy; Obstructive Sleep Apnea; OSA

Abbreviations

AED: Antiepileptic Drug; AHI: Apnea-Hypopnea Index; CHF: Congestive Heart Failure; CPAP: Continuous Positive Airway Pressure; DM: Diabetes Mellitus; MOA: Mechanism of Action; OSA: Obstructive Sleep Apnea; PSG: Polysomnography; PWE: People with Epilepsy

Introduction

Obstructive sleep apnea (OSA), characterized by the reduction of airflow during sleep, is a common disease, affecting approximately 2-7% of adults in the general population [1]. In people with epilepsy (PWE), prevalence rates are even greater, ranging from 13-80% [2]. Untreated OSA is associated with elevated mortality and morbidity, including hypertension, stroke, and metabolic dysfunction [Punjabi 2000]. In PWE, additional risks include seizure exacerbation and increased epileptogenicity [2,3].

Seizure-related consequences of OSA have most frequently been studied using PWE and OSA as their own controls [4,5]. Though sensitive to individual variation, single-subject research design is difficult to generalize [6]. For example, patients who agree to and are compliant with continuous positive airway pressure (CPAP) may possess other characteristics that affect sequelae of their seizures which are unrelated to CPAP itself, confounding the impact that OSA may have on disease control. In this regard, the literature comparing characteristics of PWE and OSA to PWE without OSA is limited.

The aim of this study was to determine whether seizure-related characteristics differ between PWE and OSA and PWE without OSA.

Methods

A retrospective study of consecutive PWE ≥ 18 years of age who were referred for evaluation of suspected OSA was performed at a single academic center. Subjects underwent diagnostic polysomnography between January 1, 2011 – January 1, 2016. The study was approved by the site institutional review board.

Potential subjects were identified via electronic search for the ICD-10/ICD-9 and CPT codes for sleep apnea, polysomnography (PSG), and epilepsy. Search terms for sleep apnea included the ICD-10 code G47.3, and the ICD-9 codes for obstructive sleep apnea (327.23), sleep related nonobstructive alveolar hypoventilation (327.27), obesity hypoventilation syndrome (278.03), sleep related hypoventilation/hypoxemia (327.26), primary central sleep apnea (327.21), Cheyne Stokes breathing pattern (786.04), central sleep apnea/complex sleep apnea (327.27), other sleep apnea (327.29), apnea not elsewhere specified (786.03) and unspecified sleep apnea (327.20). Although only subjects with OSA were included in the study, broader search terms were used to increase the sensitivity to detect patients with OSA, in order to account for any potential ICD misclassification. PSG search terms included ICD-10-PCS 4A12XOQZ, ICD-9-CM 89.17 and CPT code 95807 (sleep study, simultaneous recording of ventilation, respiratory effort, ECG or heart rate, and oxygen saturation, attended by a technologist). Epilepsy codes consisted of ICD-10 G40 and ICD-9-CM 345.

Charts were subsequently reviewed by the principal investigator to confirm that diagnostic PSG was completed during the designated dates. Charts were also individually reviewed to verify the diagnoses of epilepsy (based on the 2014 International League Against Epilepsy operational clinical definition of epilepsy [7]).
and the presence or absence of OSA (with PSG scoring based on the Center for Medicare and Medicaid Services [8] and OSA defined as per the third edition of the International Classification of Sleep Disorders [9]). Patients with a confirmed diagnosis of epilepsy who completed diagnostic PSG were included in the final analysis.

Subjects were divided into two groups: PWE without OSA, and PWE with OSA, herein referred to as (-) PWE and (+) PWE, respectively. Subgroup analysis of (-) PWE compared to (+) PWE of differing OSA severity was also performed. Based on the apnea-hypopnea index (AHI), OSA was stratified into three categories of severity: mild (5<AHI<15), moderate (15≤AHI<30) and severe (AHI≥30). Baseline characteristics were collected as follows: age at the time of diagnostic PSG, gender, body mass index, hypertension, diabetes, congestive heart failure, stroke/TIA, chronic obstructive pulmonary disease/asthma, current tobacco use, alcohol abuse, illicit substance abuse, depression, anxiety, other mood disorder, epilepsy syndrome (focal, generalized or unclassified), opioids, benzodiazepine and nonbenzodiazepine drugs, and antiepileptic drugs (AEDs).

The primary outcome measure was seizure freedom, defined as absence of all seizure types in the year preceding diagnostic PSG, including auras/focal aware seizures. Secondary outcome measures were history of generalized tonic convulsive seizures, history of status epilepticus, current number of AEDs, and primary AED mechanism of action: sodium channel (phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, rufinamide, zonisamide), GABA (phenobarbital, primidone, clobazam, valproic acid), SV2A (levetiracetam, brivaracetam), glutamate (topiramate, felbamate, perampanel), and calcium channel (gabapentin, pregabalin) [10].

Statistical Analysis

Baseline characteristics were analyzed using Pearson's χ² and independent samples t-testing, two-tailed, equal variances not assumed, as appropriate. Binominal logistic regression adjusted for significantly different baseline covariates. A p<0.05 was considered statistically significant.

Results

Demographics

Of 159 PWE referred for PSG for suspected OSA, 100 were diagnosed with OSA. Severity was mild in 44, moderate in 30, and severe in 26. (+)PWE were significantly more likely to be older and have diabetes (Table 1). Significant differences in baseline characteristics between OSA severity categories and (-)OSA are listed in table 2. Older age was more common in all OSA severity categories except severe OSA. Severe OSA was also more likely to be diabetic, male, and have congestive heart failure. Those with moderate and severe OSA were more likely to have an unclassified epilepsy syndrome. Outcomes in table 3 unadjusted and adjusted analysis, controlling for significantly different baseline features between (+) PWE and (-) PWE, was performed.

Seizure Freedom

(-)OSA were more likely to be seizure free than subjects with moderate OSA in unadjusted and adjusted analysis. There was also a trend for seizure freedom compared to all (+) PWE after a adjustment for diabetes (p = 0.057, OR = 1.986, CI = 0.978–4.033), but this did not reach significance. There was no difference in seizure freedom between those with mild and severe OSA.

History of Convulsive Seizures

There was no difference in history of convulsive seizures between (-) PWE and (+) PWE, regardless of OSA severity.

History of Status Epilepticus

There was no difference in history of status epilepticus between (-) PWE and (+) PWE, regardless of OSA severity.

Monotherapy vs. Polytherapy

In unadjusted analysis, (-) PWE were more likely to be on monotherapy compared to all (+) PWE and those with moderate OSA. This remained significant with univariate adjustment for diabetes and unclassified epilepsy, respectively, but was attenuated by age. (-) PWE were also more likely to be on monotherapy compared to the severe OSA group, controlling for unclassified epilepsy, but this did not remain significant after multivariate adjustment.

Primary AED Mechanism of Action (Tables 4 and 5)

(-)PWE were more likely to be prescribed a glutamate blocker across all degrees of OSA severity in unadjusted analysis (18/56 vs. 9/95). This remained significant after univariate and multivariate adjustment for all (+) PWE, and those with severe OSA, but was attenuated for those with mild and moderate OSA after multivariate adjustment. There was no association between OSA status and AEDs with the other mechanisms of action prescribed (sodium channel, calcium channel, GABA, SV2A).

Discussion

In this study, epilepsy patients without OSA were more likely to be seizure free, on monotherapy, and prescribed a glutamate blocking AED compared to those with OSA. Associations were attenuated by various baseline features, depending on degree of OSA severity. Overall, however, those with moderate to severe OSA demonstrated greater adverse epilepsy-related associations compared to those without OSA.

While the positive effect of CPAP on seizure control in PWE and OSA has been extensively studied [4], seizure freedom and frequency compared to PWE without OSA is less well described. Seizure freedom has demonstrated mixed associations in PWE and OSA. In a study by Pornsrisririyom, et al. there was no difference in seizure freedom between PWE and OSA without OSA [5]. Similarly, while Foldvary-Schaefer’s group found trends towards higher seizure frequency in PWE and OSA compared to those without OSA, no significant association was present for seizure freedom [11]. However, in a study examining older PWE who were divided into late-onset/worsening seizures versus seizure-free/seizure improvement, the latter group demonstrated normal mean AHIs (i.e. did not have OSA) compared to the former group, which had moderately severe OSA (with a mean AHI of 23.2) [12]. In the present study, there was a trend for seizure freedom in (-) PWE compared to (+) PWE. When more closely examined by OSA severity, (-) PWE were significantly more likely to be seizure free compared to those with moderate OSA. No difference in seizure freedom was found in comparison to those with mild OSA or severe OSA, which may be a function of limited sample size. However, a physiologic basis may also be posited. Mild OSA may not confer the a clinically significant burden to seizure control, which is in agreement with the data from Chihorek, et al. in which seizure freedom was less likely only when the mean AHI reached the moderate range [12]. This would seem to imply that greater OSA severity reduces seizure control; however, the association did not hold for those with severe OSA. A potential explanation is that the relationship between epilepsy and OSA is curvilinear or U-shaped, rather than linear, similar to cardiovascular risk factors such as hypertension and adverse health outcomes [13]. Physiologically, it may be the case
that while mild OSA does not impact seizure burden enough to be clinically significant, the seizure burden of poorly controlled PWE outweighs any additional contribution that OSA may have [14,15]. Brainstem neural circuits affecting respiration may be adversely affected by seizure activity that descends from upstream centers such as the insula or hypothalamus, with consequent ictal and post-ictal respiratory depression [16]. Putative interictal mechanisms include sleep destabilization and adverse effects on upper airway control during sleep in vulnerable patients by epileptiform discharges. As a result of such a posited U-shaped relationship, only PWE and moderate OSA would demonstrate a clinically meaningful relationship.

The evidence for an association between monotherapy and OSA is also sparse. In a study examining PWE and OSA, 15 of 30 patients were on monotherapy. However, severity of OSA in relation to the odds of monotherapy was not analyzed, and there was no comparison to PWE without OSA [17]. Chihorek’s group examined older PWE, and found that there was no difference in monotherapy rates between the group with elevated AHIs (mean AHI = 23.2) and with normal AHIs (mean AHI = 3.1) [12]. Monotherapy rates were also similar in a series by Manni, et al. (with OSA: 58.8%, without OSA: 65.4%) [18] and in an Egyptian study of epilepsy patients (with OSA: 37.2%, without OSA: 28.6, p = 0.366) [19]. In contrast, the present study showed that monotherapy was more likely in

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Table 3: Significant outcomes comparing (-) PWE to (+) PWE. (OSA: obstructive sleep apnea, DM: diabetes, CHF: congestive heart failure, AED: antiepileptic drug).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OSA Severity</th>
<th>Covariate</th>
<th>B</th>
<th>p</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure freedom</td>
<td>Moderate</td>
<td></td>
<td>1.413</td>
<td>0.019</td>
<td>4.107</td>
<td>1.263-13.357</td>
</tr>
<tr>
<td></td>
<td>Unclassified epilepsy*</td>
<td></td>
<td>1.285</td>
<td>0.034</td>
<td>3.614</td>
<td>1.102-11.859</td>
</tr>
<tr>
<td></td>
<td>Age*</td>
<td></td>
<td>1.333</td>
<td>0.031</td>
<td>3.793</td>
<td>1.130-12.724</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>Moderate</td>
<td></td>
<td>1.041</td>
<td>0.027</td>
<td>2.833</td>
<td>1.127-7.121</td>
</tr>
<tr>
<td></td>
<td>Unclassified epilepsy*</td>
<td></td>
<td>1.041</td>
<td>0.033</td>
<td>2.833</td>
<td>1.090-7.368</td>
</tr>
<tr>
<td>Seizure freedom</td>
<td>Severe</td>
<td></td>
<td>1.510</td>
<td>0.001</td>
<td>4.526</td>
<td>1.865-10.984</td>
</tr>
<tr>
<td></td>
<td>Unclassified epilepsy*</td>
<td></td>
<td>1.557</td>
<td>0.001</td>
<td>4.744</td>
<td>1.886-11.935</td>
</tr>
<tr>
<td></td>
<td>Age*</td>
<td></td>
<td>1.234</td>
<td>0.008</td>
<td>3.434</td>
<td>1.374-8.578</td>
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<tr>
<td>Glutamater blocking AED</td>
<td>OA (all)</td>
<td></td>
<td>1.132</td>
<td>0.007</td>
<td>3.713</td>
<td>1.437-9.591</td>
</tr>
<tr>
<td></td>
<td>DM*</td>
<td></td>
<td>1.227</td>
<td>0.027</td>
<td>3.411</td>
<td>1.146-10.150</td>
</tr>
<tr>
<td></td>
<td>DM, Age*</td>
<td></td>
<td>1.412</td>
<td>0.036</td>
<td>4.105</td>
<td>1.097-15.370</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td></td>
<td>2.431</td>
<td>0.022</td>
<td>11.368</td>
<td>1.424-90.771</td>
</tr>
<tr>
<td></td>
<td>Male*</td>
<td></td>
<td>2.319</td>
<td>0.030</td>
<td>10.167</td>
<td>1.251-82.613</td>
</tr>
<tr>
<td></td>
<td>DM*</td>
<td></td>
<td>2.739</td>
<td>0.025</td>
<td>15.468</td>
<td>1.409-169.816</td>
</tr>
<tr>
<td></td>
<td>CHF*</td>
<td></td>
<td>2.977</td>
<td>0.031</td>
<td>9.947</td>
<td>1.239-79.863</td>
</tr>
<tr>
<td></td>
<td>Unclassified epilepsy*</td>
<td></td>
<td>2.344</td>
<td>0.027</td>
<td>10.421</td>
<td>1.301-83.499</td>
</tr>
<tr>
<td></td>
<td>All*</td>
<td></td>
<td>2.317</td>
<td>0.048</td>
<td>10.147</td>
<td>1.020-100.897</td>
</tr>
</tbody>
</table>

Table 4: AED Primary Mechanism of Action. (AED: antiepileptic drug, MOA: mechanism of action, OSA: obstructive sleep apnea).

<table>
<thead>
<tr>
<th>Primary MOA</th>
<th>No OSA (N = 56)</th>
<th>OSA (N = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na Channel</td>
<td>40</td>
<td>68</td>
</tr>
<tr>
<td>GABA</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Ca Channel</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Glutamate</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>SV2A</td>
<td>27</td>
<td>31</td>
</tr>
</tbody>
</table>

Table 5: Individual AEDs Prescribed. AED: antiepileptic drug.
Future research could address these limitations, and include prospective studies across multiple sites.

Conclusions

Seizure freedom, monotherapy, and glutamate blocking AEDs are more common in PWE without OSA compared to those with OSA. A U-shaped relationship may exist between OSA severity and seizure freedom, and the diagnosis of unclassified epilepsy syndromes may be more likely in those with moderate and severe OSA due to age-related characteristics.

Conflict of Interest

The author has no conflicts of interest to declare.

Ethical Approval

Consent was waived by the NYU School of Medicine IRB due to the retrospective nature of the research.

References


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