



Original Article

Effect of Treatment of Obstructive Sleep Apnea on Seizure Outcomes in Children With Epilepsy

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ABSTRACT

A retrospective review of children with epilepsy and obstructive sleep apnea, treated surgically for their obstructive sleep apnea from January 2008–October 2010, was performed for age, sex, type of epilepsy, antiseizure medications, sleep-study data, and changes in seizure frequency. Twenty-seven subjects (median age, 5 years) with no adjustment to their medications around their time of surgery were identified. Three months after surgery, 10 (37%) patients became seizure-free, three (11%) demonstrated >50% seizure-reduction, and six (22%) exhibited an amelioration of seizure frequency. Two (7%) demonstrated unchanged seizure-frequency, and six (22%) manifested a worsening of seizure frequency. Median seizure frequency before surgery was 8.5 (interquartile range, 2–90), and after surgery, three (interquartile range, 0–75), with a 53% median seizure reduction. Multivariate analysis demonstrated a trend toward seizure freedom with each percentile increase in body mass index and early age of surgery. We conclude that obstructive sleep apnea surgery may decrease seizure frequency, especially in children with elevated body mass index scores and younger age at time of surgery.

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Introduction

The coexistence of epilepsy and obstructive sleep apnea has been well described. The prevalence of obstructive sleep apnea in patients with epilepsy was reported to be approximately 10% in adults [1] and 20% in children [2]. Obstructive sleep apnea in adults is typically treated with nocturnal continuous positive airway pressure, and with tonsillectomy and adenoidectomy in children. Untreated obstructive sleep apnea worsens seizure control [3]. Furthermore, uncontrolled series and randomized pilot trials demonstrated the benefits of continuous positive airway pressure on seizure frequency in adults (Table 1) [4–7].

Little information is available regarding the effects of tonsillectomy and adenoidectomy on seizure frequency in children with obstructive sleep apnea and epilepsy. Koh et al. described the benefits of surgical intervention on seizure frequency in nine children with obstructive sleep apnea [8]. Malow et al. reported on a child with a 45% seizure reduction after bilevel positive airway therapy [7].

This study further assesses the effects of obstructive sleep apnea surgery, and identifies factors that increase the likelihood of seizure reduction in pediatric epilepsy.

Methods

We undertook a retrospective review of clinical and polysomnographic data of children (0–18 years old) with epilepsy who underwent surgery for obstructive sleep apnea between 2008 and 2010, using a computerized search for diagnoses of epilepsy and surgery (tonsillectomy and adenoidectomy; International Classification of Diseases codes 345 and 28, respectively). Patients with fewer than two unprovoked seizures, no seizures for 2 years before surgery, no clinic visits or medication adjustments 3 months before or after their intervention, and with epileptic encephalopathy (i.e., Landau-Kleffner syndrome, continuous spikes and slow waves during sleep) were excluded. Data on age at onset of epilepsy, age at surgery, body mass index with z-scores, type of surgery (adenoidectomy, tonsillectomy, or tonsillectomy and adenoidectomy), the etiology of epilepsy (unknown, structural/metabolic, and epilepsy syndrome) [9], the localization of epilepsy (generalized or focal) [9], seizure type (partial or generalized tonic-clonic), medications at time of surgery, polysomnographic data before and after surgery (apnea-hypopnea index, apnea severity, and maximum desaturation), and seizure frequency before and after surgery were collected.

Overnight polysomnographic data, before or after surgery or both, were also included. Polysomnography was performed using digital polysomnographic equipment (Sleep Scan Vision 2 Polysomnography; Biologic System Corporation, Mundelein, IL). Further details on the acquisition of polysomnographic data are described elsewhere [2].

Apnea-hypopnea index scores were classified as mild (1–5/hour), moderate (5–10/hour), and severe (≥ 10 /hour). Desaturation was defined as mild (85–92%), moderate (85–80%), and severe (<80%).

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Table 1. Literature review of previous studies demonstrating the effects of OSA treatment on seizure outcomes

	Population Sample	Intervention	Results
Devinsky et al., 1994 [4]	Seven adults with OSA and epilepsy (aged 23–75 years)	Treated with CPAP (n = 4), protriptyline (n = 2), or tracheostomy (n = 1)	Six of seven patients experienced an improvement in seizure frequency. Patients treated with protriptyline (n = 2) and tracheostomy (n = 1) also underwent changes in AED regimen before decrease in seizure frequency. Three of four patients with CPAP experienced seizure reduction.
Malow et al., 2003 [7]	Six adults (aged 28–56 years) and three children (aged 14–16 years) with OSA	Five adults treated with CPAP, and one with an oral appliance; three children treated with BiPAP (n = 1) and CPAP (n = 2)	Two adults and 2 children (both receiving CPAP) did not complete the study. The three adults and one child who were compliant with CPAP experienced at least a 45% reduction in seizure frequency. No change was evident in the patient with an oral appliance.
Koh et al., 2000 [8]	Nine children (aged 1.1–6.7 years) with metabolic disorders (n = 2), structural abnormalities (n = 3), or infectious (n = 1) and genetic (n = 3) abnormalities	One child treated with TA, three with tonsillectomy, two with tracheostomy, one with adenoidectomy, one with oxygen, and one with uvullectomy	Fifty-six percent (n = 5) of patients demonstrated a reduction in seizure frequency.

Abbreviations:
AED = Antiepileptic drug
BiPAP = Bilevel positive airway pressure
CPAP = Continuous positive airway pressure
OSA = Obstructive sleep apnea
TA = Tonsillectomy and adenoidectomy

Seizure frequency after surgery was assessed during clinic visits. Significant seizure reduction was defined as $\geq 50\%$ seizure reduction over a 3-month period after surgery. Seizure amelioration was defined as any reduction in seizure frequency.

Statistical analysis was performed with nonparametric measures, using χ^2 tests for contingency tables with the Wilcoxon matched-pairs, signed-rank test and the Wilcoxon two-sample test (SPSS version 16.0, SPSS, Inc., Chicago, IL). When appropriate, odds ratios were calculated, with 95% confidence intervals, and significance was set at $P < 0.05$. The effect of several independent variables was assessed using multiple logistic regressions. Decisions about which terms to include were based on likelihood ratio tests and Akaike's information criteria. The reported confidence intervals were obtained using the criteria of Wald.

Results

Of 4600 patients who underwent obstructive sleep apnea surgery during the study period, 269 had a history of seizures, 57 manifested epilepsy with seizure frequency and polysomnographic data available before and after tonsillectomy and adenoidectomy, and 27 (median age, 5 years) received no adjustment to their antiepileptic drugs, 3 months before or after surgery (Table 2).

Epilepsy etiologies included 11 unknown (primary generalized epilepsy), six genetic and clinical epilepsy syndromes (including benign rolandic epilepsy of childhood and Doose syndrome), and 10 symptomatic structural/metabolic cases of seizures (including diffuse hypoxic ischemic injury or strokes). Overall, we included 16 subjects with generalized epilepsy and 11 with focal epilepsy.

The presurgery mean score for the apnea-hypopnea index was 7/hour (range, 5–17/hour), with mean desaturation down to 88% (range, 80–94%) during obstructive events, which improved after surgery to a mean apnea-hypopnea index of 2/hour (range, 0–6/hour; $P < 0.04$), with mean desaturation down to 96% (range, 88–99%; $P < 0.03$) during residual obstructive events.

Three months after surgery, 10 (37%) patients became seizure-free, three (11%) demonstrated a seizure reduction of $>50\%$, and six (22%) demonstrated an amelioration of seizure frequency. Two exhibited unchanged seizure frequency (7%), and six (22%) experienced a worsening of seizure frequency. The median seizure frequency before tonsillectomy and adenoidectomy was 8.5 (interquartile range, 2–90), whereas the median seizure frequency after tonsillectomy and adenoidectomy was 3 (interquartile range, 0–75), with a 53% median seizure reduction. Although a strong trend existed, there was no statistical significance in obstructive sleep apnea surgery leading to seizure reduction or freedom.

Multiple logistic regression analysis demonstrated a trend toward seizure freedom with each percentile increase in body mass index and younger age at time of surgery. The odds of becoming seizure-free increased by a factor of 1.04 (95% confidence interval, 0.99–1.1) for each unit increase in body mass index ($P = 0.099$). The younger the age at time of surgery, the more likely that patients would become seizure-free (odds ratio, 0.75; 95% confidence interval, 0.56–1.02; $P = 0.0738$). In this analysis, age was treated as a continuous variable and was not divided into groups (e.g., 0–3, 3–6, and 6–12 years) because of the small sample size.

The six subjects with seizure exacerbation after tonsillectomy and adenoidectomy manifested progressive epilepsy syndromes (neurometabolic syndromes, n = 3; known catastrophic epilepsy syndromes, n = 3). Of the patients with an amelioration in (or unchanged) seizure frequency (n = 21; median age, 5.75 years), the median seizure frequency before tonsillectomy and adenoidectomy was 8 (interquartile range, 2.0–67.5). After tonsillectomy and adenoidectomy, the median seizure frequency was 0.5 (interquartile range, 0–13; $P < 0.01$), with an 87% median seizure reduction. Multivariate analysis in this cohort confirmed similar trends toward improvement in more obese individuals (odds ratio, 1.03; 95% confidence interval, 0.99–1.08).

Discussion

In our population, obstructive sleep apnea surgery provided a reduction in seizure frequencies for children who did not manifest a progressive epilepsy syndrome. For all patients with epilepsy, a strong trend toward seizure reduction after surgery was evident. To our knowledge, this report is the first of seizure reduction after obstructive sleep apnea surgery in children with nonprogressive epilepsy syndromes. Unlike other pediatric studies, we were able to identify factors that increased the likelihood of seizure reduction, i.e., high body mass index scores and younger age at time of surgery.

Obstructive sleep apnea has been hypothesized to exacerbate seizure frequency by disrupting rapid eye movement sleep, thereby increasing the amount of lighter non-rapid eye movement sleep as well as daytime sleepiness, which are highly activating states for patients with epilepsy [10]. The adult and pediatric literature demonstrates the ameliorating effects of obstructive sleep apnea treatment on seizure frequency. Our study confirms that the

Table 2. Clinical characteristics of all patients

Boys/girls	17/10
Mean age at onset (years)	2.86 (range, 0-13)
BMI percentile, median (IQR)	82.86 (62.63-93.26)
Surgery type	
TA	23
Adenoidectomy	4
Tonsillectomy	0
Etiology of epilepsy	
Unknown	11
Genetic causes and clinical epilepsy syndromes	6
Structural/metabolic	10
Progressive epilepsy syndromes	6
Semiology of seizures	
SPS	0
CPS	11
GENa	6
GENb	10
AEDs per patient	
No AEDs	0
One AED	12
Two AEDs	8
Three or more AEDs	7
Mean age at time of surgery (years)	5.97 (range, 1.3-18)
Monthly median seizure frequency of all patients presurgery (IQR)	8.5 (2-90)
Monthly median seizure frequency of all patients after surgery (IQR, <i>P</i>)	3 (0-75, >0.05)
Seizure-free (%)	10 (37)
Seizure amelioration (%)	6 (22)
≥50% seizure reduction (%)	3 (11)
Seizure exacerbation (%)	6 (22)
No change (%)	2 (7)
Patients with nonprogressive epilepsy (<i>n</i>)	21
Monthly median seizure frequency in nonprogressive patients (IQR)	8 (2-67.5)
Monthly median seizure frequency in patients with nonprogressive epilepsy (IQR, <i>P</i>)	0.5 (0-13, <0.01)
Seizure-free (%)	10 (47)
Seizure amelioration (%)	6 (29)
≥50% seizure reduction (%)	3 (14)
No change (%)	2 (10)
Abbreviations:	
AED	= Antiepileptic drug
BMI	= Body mass index
CPS	= Complex partial seizures
GENa	= Generalized tonic-clonic seizures
GENb	= Absence, tonic, myoclonic, and atonic seizures
IQR	= Interquartile range
PSG	= Polysomnography
SPS	= Simple partial seizures
TA	= Tonsillectomy and adenoidectomy

surgical treatment of pediatric obstructive sleep apnea can lead to a significant seizure reduction in patients with nonprogressive epilepsies.

This study also identifies factors that increase the likelihood of seizure reduction and seizure freedom after this intervention. Patients with high body mass index scores are more likely to experience an improvement in seizure frequency, compared with those who are within normal range. This finding can be ascribed to an increased severity of obstructive sleep apnea in children with a high body mass index [11].

Obstructive sleep apnea is very common at ages 3–6 years because of enlarged tonsils and adenoids. Hence, younger patients in this age group improved the most [12]. Patients with obstructive sleep apnea have a unique opportunity to experience significant seizure reduction by undergoing surgery early in life. We also speculate that the reduction of seizure frequency in patients who receive surgery earlier in life is most likely attributable to improved stability in the sleep/wake cycle, which decreases the window of opportunity to manifest a seizure.

Patients with progressive epilepsy will continue to exhibit seizures unabated, and based on our findings, it remains unclear whether seizure frequency is unlikely to be ameliorated by obstructive sleep apnea surgery, or if improvement was overshadowed by a progressive worsening of the underlying epilepsy syndrome. Although six patients in our study manifested seizure exacerbations, these exacerbations were likely related to the underlying epilepsy syndrome, rather than the surgical procedure.

Previous studies (Table 1) demonstrated the effectiveness of obstructive sleep apnea treatment on seizure control in children and adults with epilepsy. However, some of these data are confounded by noncompliance and changes in antiepileptic drug management either immediately before or after obstructive sleep apnea treatment. Less is known about obstructive sleep apnea surgery compared with noninvasive therapies. Our study confirms the reduction in seizure frequency in children after obstructive sleep apnea surgery. In addition, our study contributes to this body of work by identifying risk factors that increase the likelihood of seizure reduction.

This study must be interpreted in the appropriate clinical context, considering its retrospective nature, short duration of follow-up, and small sample size. Although all patients received a clinical diagnosis of obstructive sleep apnea, many did not undergo polysomnography before and after surgery. In addition, the confounding effects of noncompliance with antiepileptic drugs and accurate seizure counts in a retrospective analysis cannot be excluded.

Conclusion

Our study demonstrates that obstructive sleep apnea surgery may be considered in an attempt to decrease seizure frequency, especially among those with elevated body mass index scores and younger age at time of surgery. Clinicians should consider screening for and confirming diagnoses of obstructive sleep apnea, especially in obese children with epilepsy, followed by surgery to treat their obstructive sleep apnea, so as to improve seizure outcomes and daytime alertness, sleep quality at night, and overall quality of life. Larger, prospective multicenter studies should be performed on all children with epilepsy to validate our observations, including subset analyses of patients with progressive epilepsy syndromes to determine whether worsening seizure frequency in these patients is related to worsening seizures and the progression of their underlying etiology and syndrome.

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