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Editorial

Obstructive sleep apnea in patients with epilepsy: does treatment affect seizure control?

In this issue of *Sleep Medicine*, Malow and colleagues [1] prospectively studied the effect of treating obstructive sleep apnea (OSA) on seizure frequency in patients with epilepsy. Only those having four or more seizures per month and meeting the authors' established cutoffs on the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ) [2] for adults and the sleep related breathing disorder (SRBD) subscale of the Pediatric Sleep Questionnaire [3] for children were invited to participate in the study. A total of 444 subjects (including 46 children) were surveyed. Thirteen adults and five pediatric patients agreed to participate and underwent baseline polysomnogram (PSG) and multiple sleep latency test (MSLT). Six adults and three children met criteria for OSA. The apnea–hypopnea index (AHI) ranged from 10.1 to 35.1 in adults and 3.8–5.3 in children. Seizure frequency was prospectively monitored during treatment with CPAP (five adults and three children) or oral appliance (one adult) for at least 8 weeks while antiepileptic drug (AED) therapy remained constant. At the end of the treatment phase, subjects underwent repeat PSG/MSLT. Only four adults (including the one with an oral appliance) and one child were compliant with treatment. The three adults treated with CPAP reported at least a 45% reduction in seizure frequency; seizure control remained the same in the subject treated with an oral appliance, although nocturnal seizures decreased. In the only child compliant with CPAP, a 60% reduction in atonic seizures was achieved and myoclonic seizures remained unchanged.

This study extends prior reports suggesting improved seizure control with treatment of OSA in patients with epilepsy [4–7]. Devinsky and colleagues treated seven adults with focal epilepsy and moderate to severe OSA with CPAP (3), CPAP with weight reduction (1), CPAP with pharmacotherapy (1), pharmacotherapy alone (1) and tracheostomy with supplemental oxygen and acetazolamide (1) [4]. Treatment produced a 50% or greater reduction in seizures in six cases. However, three of five patients prescribed CPAP were noncompliant. In an earlier study by Malow and colleagues [5], CPAP/BIPAP was prescribed in 28 patients with epilepsy and OSA; however, only 54% of patients were compliant. Seizure control improved in five of nine patients having seizures before treatment. In two cases, Excessive Daytime Sleepiness improved despite higher doses of AEDs or the introduction of new AEDs. In a third series, four of 10 patients with OSA experienced a dramatic improvement in seizures (three became seizure-free) with CPAP or positional therapy [6]. Seizures occurred exclusively on awakening or in sleep in three of the four patients experiencing the greatest seizure reduction. A typical body habitus of OSA was present in only two cases. Seizure frequency was reduced in three other patients when AED adjustments were also made. In a pediatric series, seizure control improved significantly in six out of 10 children with epilepsy and OSA following tonsillectomy (8), tracheostomy (1) or CPAP (1) [7].

As the authors of this report correctly point out, prior studies are limited by small and biased samples and were not prospective in nature. Only selected subjects treated for OSA are reported. With one exception, AED therapy was not monitored [6]. The current study is also limited by a low participation rate. Of over 400 potential subjects, 62 met enrollment criteria but only 18 agreed to participate, and of these only nine had OSA on baseline testing and were treated. Furthermore, only five of the nine were compliant with therapy. In addition, the patients who did improve had relatively low AHIs (10.1–27.2). Of three adults with pre- and post-treatment MSLTs, mean sleep latency improved in only one case, suggesting that the change in seizure frequency may be due to placebo effect or represent a random fluctuation in seizure control. Patients with epilepsy commonly report spontaneous changes in seizure frequency, often without apparent explanation.

As the authors also emphasize, the diagnosis of OSA in patients with frequent seizures is not always straightforward. Daytime sleepiness, frequent awakenings, early morning awakenings and difficulty initiating sleep are common complaints of adults [8,9] and children [10] with epilepsy. While sleep disturbances seem to be more common in patients with poorer seizure control [11], sleep architecture is disrupted even in the absence of seizures and AEDs [12]. Poor sleep hygiene practices are common among patients with epilepsy and represent another cause of hypersomnia [11,13]. Both nocturnal and daytime seizures adversely affect sleep. AED therapy also affects sleep quality and daytime vigilance. Whether primary sleep disorders represent a significant cause of EDS in patients with epilepsy remains to be determined.

The prevalence of sleep-disordered breathing in the epileptic population appears to exceed that of the general

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population. In the only prospective study, PSGs were performed in 39 patients with medically refractory epilepsy without a history of sleep disorders [14]. OSA was identified in 13 (33%) cases, including 50% of males and 19% of females. The disorder was moderate to severe (AHI $>$ 20) in five cases. Patients with OSA were more likely to be males and to have a higher body mass index (BMI), history of snoring or witnessed apnea and nocturnal seizures. Seizure frequency, localization, type and number of AEDs and Epworth Sleepiness Scale scores did not differentiate those with significant OSA from the other subjects.

Several mechanisms may explain the increased prevalence of sleep-disordered breathing in the epileptic population. Weight gain is associated with AED therapy, most notably valproic acid and carbamazepine in both children [15] and adults [16,17]. Relatively modest weight gain may lead to clinically significant sleep-disordered breathing, particularly in predisposed individuals. In a recent, prospective, randomized trial including nearly 700 adults, weight change positively correlated with change in AHI over time, when adjusting for gender, age and smoking habits [18]. At the lower range of AHI, each 1% change in weight was associated with a 3% difference in AHI. Therefore, an increase in body weight of 10% resulted in an increase in AHI of 30%. Individuals with epilepsy are also less physically fit than age-matched controls as demonstrated by significant differences in aerobic endurance, muscle strength endurance and flexibility and greater BMI [19,20]. AED therapy may negatively affect upper airway tone; whether central mechanisms related to epilepsy affect the upper airway remains unknown. Endocrine disorders, including hypothyroidism and polycystic ovarian syndrome (PCOS) have also been associated with AED therapy. An increased prevalence of OSA was recently reported in women with PCOS [21,22].

An estimated 30–40% of patients with epilepsy fail to achieve a seizure-free state with medical therapy [23]. Sleep is important for patients with epilepsy and factors adversely affecting sleep including seizures, medications, poor sleep hygiene and primary sleep disorders might be expected to compromise seizure control. Addressing sleep complaints, therefore, represents a logical treatment option in the medically refractory epilepsy population that has not been adequately explored in the past. Malow and colleagues highlight some of the challenges in this area of research. A larger, prospective, randomized, placebo-controlled study is needed to determine the effect of treatment of primary sleep disorders on seizures in patients with epilepsy.

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