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Impact of vagus nerve stimulation on sleep-related breathing disorders in adults with epilepsy

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ABSTRACT

Background: Vagus nerve stimulation (VNS) can induce a sleep apnea syndrome (SAS), which in turn can worsen seizure control and represents a cardiovascular risk factor. Epidemiology of VNS-induced SAS has received little attention to date. The purpose of this study was to estimate the VNS-induced SAS prevalence and to explore clinical variables potentially correlating with its development.
Methods: We analyzed the computerized medical records of 18 consecutive adults treated for refractory epilepsy with VNS, implanted between May 2008 and October 2015. Patients underwent sleep polygraphy or polysomnography before and after VNS implantation. Between patients with and without SAS, we compared variables related to epilepsy type and device parameters.
Results: Two patients had SAS and were treated before implantation; one improved after VNS, the other worsened. Four other patients developed SAS after VNS: induced/aggravated SAS occurred in 5/18 patients (prevalence: 27.8%). Only 2 of them had symptoms: one complained of important snoring, the other reported seizure worsening. All 5 patients were successfully treated by combinations of continuous positive airway pressure (cPAP), positional therapy, or VNS parameters modification. There was no statistically significant difference between potential predictors.
Conclusion: Despite the relatively modest clinical impact on epilepsy, in view of the associated cardiovascular risk factor development, easy treatment, and the relatively high SAS prevalence, routine screening for SAS before and after VNS implantation may represent a reasonable practice.

1. Introduction

Vagus nerve stimulation (VNS) is a palliative therapy for refractory epilepsy; it is used since more than 20 years and is regarded as safe, well tolerated, and effective [1–5]. A seminal study about the effect of VNS on sleep [6] analyzed polysomnographies (PSG) of four patients with VNS before and after treatment, showing that the apnea-hypopnea index (AHI) was significantly higher with activated VNS; several subsequent observations found comparable results [7–10]. Vagus nerve stimulation seems to increase both respiratory effort and airways obstruction during its activation [6,7,9–13]. Both peripheral and central mechanisms represent possible explanations for changes in respiratory patterns. The former would be triggered by stimulation and subsequent narrowing of the upper airways musculature [6,7,12,14]. Since the vagus nerve has projections to the brainstem respiratory control centers [6,7,12,14], a central inhibition of respiratory drive could also be observed.

Even if changes in respiratory patterns are found in many patients, they do not seem clinically relevant in most. While the majority of studied patients shows changes in respiratory patterns (34–100%), only 0–33% develop sleep-apnea syndrome (SAS) [7,12,13,15]. To date, however, the prevalence of SAS in patients with VNS remains largely unknown, because of the fact that the aforementioned studies included relatively small groups of patients selected from a sleep medicine angle, who are not necessarily representative of the whole population of patients with epilepsy implanted with VNS. Nevertheless, VNS-related SAS seems to be frequent enough that sleep study screening before implantation is considered [8,9,12,13,16,17]. Assessments after implantation could also be important, in as much as VNS increases wakefulness [18], which could mask one of the cardinal symptoms of SAS, daytime somnolence [6,19,20].

While lacking an evidence-based approach, many treatment options have been described for patients with VNS-related SAS: continuous positive airway pressure (cPAP) [8,9,13,14,16,17,21]; positional therapy [8,9]; and changes in stimulator settings (especially increasing OFF time or decreasing stimulation frequency) [6,8,16,17,22]. It has been suggested that VNS parameter modifications might further enhance the cPAP impact [14]. In severe cases, VNS deactivation at night has been proposed [8,16,17]. Treating SAS seems important not only for the quality of life, but also because sleep disruption can increase seizure frequency [6,8,17], on top of representing an independent cardiovascular risk factor [19,23].

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To summarize, a link between the VNS and sleep respiratory disorders is described but the prevalence of this side effect is unknown. Clinical variables potentially associated with it have not been clearly elucidated to this day, with only one recent study postulating left vocal cord abduction as a predisposing factor [17].

2. Methods

This is a retrospective cohort study assessing the prevalence of VNS-induced SAS, and exploring potential clinical variables correlating with its development. The study was approved by our ethics committee.

We analyzed the computerized medical records of consecutive adults (>18 years old) implanted with VNS for refractory epilepsy at our center between May 2008 and October 2015; follow-up extended until May 2017. Sleep recordings took place in our sleep center (polysomnography, PSG) or at home (sleep polygraphy (PG)), in accordance with the American Academy of Sleep Medicine's 2007 recommendations [24]. Apnea was defined as a decrease of at least 90% of airflow from baseline, lasting 10 s or longer, while hypopnoeas were scored according to the 2012 American Academy of Sleep Medicine criteria (≥30% decrease of airflow lasting at least 10 s, associated with either arousal or a ≥3% O_2 saturation decrease) [25]. All studies but one were conducted at our sleep center and interpreted by the last author, a sleep certified neurologist. Most studies were ambulatory PG, chosen as they are more convenient than PSG both for patients and reimbursement, while retaining comparable sensitivity in SAS diagnosis [26,27]. All patients underwent a sleep study before implantation to screen for SAS, as this would have needed specific treatment. They also underwent a control sleep study after implantation. The mean number of apnoeas and hypopnoeas per hour of sleep (apnoea-hypopnoea index [AHI]) was calculated. Sleep apnea syndrome was defined after [16] (mild: AHI = 5–10/h; moderated: AHI = 10–15/h; severe if AHI ≥ 15). We stratified the cohort in two groups: patients who worsened already existing SAS or developed it after implantation and patients without SAS worsening or development.

We compared several potential explanatory variables related to SAS development between the two groups: demographics, being overweight (defined as a body-mass-index > 25), history of arterial hypertension or diabetes, variables related to epilepsy diagnosis (main seizure types—focal or generalized, percentage of VNS related decrease in seizures frequency, presence of valproate, VPA, in current medication), and VNS parameters (current intensity, pulse frequency, duration, and ON and OFF times). We also compared the reported magnet efficacy (defined as an effect in at least 30% of seizures in terms of shortening of the episode or of the postictal state) and a subjective significant increase in vigilance (reported by the patient or relatives/caregivers).

Given the small groups of patients, Fisher's exact tests were used to analyze dichotomous variables, and Mann–Whitney *U* tests for

Table 1
Clinical characteristics of all patients.

No.-age-gender	Epilepsy type	Etiology	% Reduction of seizures with VNS	Parameters of VNS device (at time of the sleep study)	Medication	
1. 50-F	Focal	Adult rasmussen encephalitis	>75%	2.5 mA, 30 Hz, 250 μs, 30 s on, 05 mn off	LTG, PGB, LEV, CLZ	*
2. 34-F	Focal/generalized	Ring 20 chromosome	0%	0.5 mA, 20 Hz, 250 μs, 30 s on, 5 mn off	OXC, CLZ	
3. 27-M	Generalized	Dravet syndrome	>75%	2.25 mA, 20 Hz, 250 μs, 30 s on, 5 mn off	PHT, VPA, LEV, CLZ	
4. 31-F	Focal	Unknown	>75%	2 mA, 20 Hz, 250 μs, 21 s on, 0.8 mn off	LTG, FBM, PGB	*
5. 39-M	Generalized	Unknown	>50%	1.75 mA, 20 Hz, 250 μs, 30 s on, 5 mn off	VPA, LEV, LTG, CLZ	
6. 37-M	Focal	Polymicrogyria	0%, shorter	2.25 mA, 30 Hz, 250 μs, 30 s on, 1.8 mn off	LTG, VPA, CLBZ	
7. 52-F	Focal	Hippocampus sclerosis	0%	2 mA, 20 Hz, 250 μs, 30 s on, 1.8 mn off	LTG, TPM	
8. 52-M	Focal	Perinatal hypoxia	0%, shorter	1.75 mA, 20 Hz, 250 μs, 30 s on, 5 mn off	LEV, PGB	
9. 26-M	Focal	Focal cortical dysplasia	>90%	2 mA, 20 Hz, 250 μs, 7 s on, 0.3 mn off	PHT, OXC, RTG, CLZ	*
10. 35-F	Focal	Hippocampus sclerosis	50%, shorter	1.75 mA, 20 Hz, 250 μs, 30 s on, 5 mn off	CBZ, TPM, PGB	
11. 28-F	Focal	CDKL5	>70%, shorter	1.5 mA, 20 Hz, 250 μs, 30 s on, 5 mn off	LTG, VPA, CLBZ	
12. 31-M	Generalized	Unknown	>90%	1.5 mA, 20 Hz, 250 μs, 30 s on, 5 mn off	VPA, RUF, ZNS	
13. 26-F	Focal	Perinatal hypoxia	50%	1.75 mA, 20 Hz, 250 μs, 30 s on, 1.8 mn off	OXC, LTG, LEV	*
14. 25-M	Focal/generalized	Unknown	>50%	1.75 mA, 20 Hz, 250 μs, 30 s on, 1.1 mn off	TPM, OXC, RUF, CLZ	
15. 34-M	Generalized	Unknown	>50%	2 mA, 20 Hz, 250 μs, 30 s on, 3 mn off	PB, RUF, CLBZ	*
16. 25-M	Generalized	Unknown	>90%	1.25 mA, 20 Hz, 250 μs, 30 s on, 5 mn off	LTG, TPM, VPA	
17. 23-M	Focal	Focal cortical dysplasia	>75%	1.5 mA, 30 Hz, 250 μs, 30 s on, 5 mn off	LEV, CBZ, TPM, PER	
18. 22-M	Generalized	Unknown	>90%	1.25 mA, 20 Hz, 250 μs, 30 s on, 1.1 mn off	VPA, OXC, SUL, CLZ	

*Patients 1, 4, 9, 13, and 15 (highlighted lines) were suffering from SAS induced/aggravated by VNS.
CLBZ: clobazam, CLZ: clozapine, LTG: lamotrigine, LEV: levetiracetam, FBM: felbamate, OXC: oxcarbazepine, PER: perampanel, PB: phenobarbital, PHT: phenytoin, PGB: pregabaline, RTG: retigabine, RUF: rufinamide, VPA: valproic acid, ZNS: zonisamide.