Clinical commentary

Epileptic Disord 2020; 22 (6): 790-6

Complex sleep-disordered breathing after vagus nerve stimulation: broadening the spectrum of adverse events of special interest

Miguel Oliveira Santos [1,2], Carla Bentes [1], Tiago Teodoro [1,3,4], Susana Moreira [5,6], Marta Marques [7], Diogo Tomé [7], Ana Rita Peralta [1,2]

[1] Department of Neurosciences and Mental Health, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal
[2] Institute of Physiology Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Portugal
[3] Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's, University of London & Department of Neurology, St George's University Hospitals NHS Foundation Trust, London, UK
[4] Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Portugal
[5] Department of Thorax, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal
[6] Instituto Gulbenkian Ciência, Oeiras, Portugal
[7] Department of Otorhinolaryngology, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

Received April 10, 2019; Accepted August 09, 2020

ABSTRACT – Two young males with refractory epilepsy of unknown aetiology were referred for vagus nerve stimulation (VNS). Sleep disturbances emerged following VNS parameter changes. In Patient 1, video-polysomnogram (PSG) disclosed snoring and catathrenia in non-REM sleep. Central apnoea also occurred, but more rarely. In Patient 2, video-PSG showed mixed apnoea with desaturation and episodes of stridor followed by a catathrenia-like sound. A drug-induced sleep endoscopy (DISE) revealed, during VNS OFF time, glossoptosis, "trap door" of the epiglottis, and paresis of the left side of the larynx and ipsilateral vocal cords. During ON time, there were periods of pharyngeal collapse, in which video-PSG revealed patterns suggestive of both obstructive and central sleep apnoea. All these sleep-related phenomena were coincident with VNS ON time. In the first patient, VNS parameter adjustment was sufficient to successfully reverse all the symptoms, whereas the other patient required concomitant treatment with continuous positive airway pressure. The data broaden our knowledge about sleep disorders related to VNS, in particular stridor and catathrenia. We suggest that central sleep apnoea may be associated with laryngeal occlusion. DISE may be considered in selected cases

VIDEOS ONLINE

Correspondence:
Miguel Oliveira Santos
Department of Neurosciences and Mental Health, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal
Institute of Physiology Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Portugal
<migueloliveirasantos@hotmail.com>

doi:10.1684/epd.2020.1223

as a valuable clinical tool to evaluate, in a single session, the effectiveness of multiple VNS parameter changes on respiration and laryngeal side effects. [*Published with video sequences*].

Key words: stridor, catathrenia, central sleep apnoea, sleep-breathing disorder, vagus nerve stimulation

Vagus nerve stimulation (VNS) can be used in parallel with drug therapy as adjuvant treatment for refractory epilepsy, and is reported to lead to a 50% decrease in seizures in 35-45% adult epileptic patients (Parhizgar *et al*., 2011). Common side effects associated with the stimulation of vagus nerve afferent fibres include respiratory and gastrointestinal tract symptoms, and in some cases, also development of sleep-breathing disorders (SBD) such as obstructive, and less frequently, central sleep apnoea (Malow *et al*., 2000; Holmes *et al*., 2003; Marzec *et al*., 2003; Nagarajan *et al*., 2003; Papacostas *et al*., 2007; Hsieh *et al*., 2008; Parhizgar *et al*., 2011; Zambrelli *et al*., 2016; Forde *et al*., 2017). To date, the prevalence of sleep disturbances in patients with VNS remains to be elucidated. Contrary to well-known VNS-induced sleep apnoea, the association between VNS and stridor has been seldom documented and no previous case of catathrenia has been previously described.

Case study

We describe two young males (34 and 23 years old) with refractory epilepsy since childhood, who were referred for palliative epilepsy surgery with VNS with good clinical response.

The older patient (Patient 1) had no known aetiology for his epilepsy. He had focal to bilateral tonic-clonic seizures. Physical examination was normal. Body mass index (BMI) was 24.6 Kg/m^2. Video-EEG showed a bilateral frontal, fronto-central and fronto-temporal ictal origin. Brain MRI was unremarkable. SPECT revealed left temporo-occipital hypoperfusion. The patient was treated with palliative surgery with VNS. After increasing current output from 1.50 to 1.75 mA, he started to experience episodes of daytime involuntary throat movements, and his partner complained of abnormal nocturnal noises. These symptoms worsened after reducing VNS OFF time from 3.0 to 1.8 min. Direct video-laryngoscopy during wakefulness showed mild left vocal cord paresis during VNS OFF time and ipsilateral laryngeal tilt during ON time (*videos 1 and 2*). A nocturnal video-polysomnogram (PSG) disclosed flow limitation without awakening or oxygen desaturation (respiratory disturbance index [RDI]: 5.7/h; oxygen desaturation index [ODI]: 2.04/h), snoring (inspiratory and expiratory) and recurrent episodes of prolonged expiratory groaning occasionally accompanied by a bradyarrhythmic respiration pattern (catathrenia) in non-REM sleep (REM sleep was not detected in this sleep study) (*figure 1*). The catathrenia sounds were not as long-lasting as usually reported in the literature. They could last from two to five seconds and occurred at variable intervals after the stimulation started (*audios 1, 2 and 3*). Central apnoea also occurred, but much more rarely. All these sleep-related respiratory phenomena were coincident with VNS ON time. VNS parameter adjustment relative to previous values (current output of 1.50 mA and OFF time of 3.0 min) successfully reversed all the symptoms.

The second patient (Patient 2) had acute viral meningoencephalitis at the age of five, complicated by focal epilepsy with focal to bilateral tonic-clonic seizures and mild-to-moderate cognitive impairment. His BMI was 21.2 Kg/m^2. Video-EEG showed seizures with multiple ictal onset zones (left fronto-temporal, right frontal and right temporal). Brain MRI was normal. SPECT disclosed diffuse hypoperfusion of the right cerebral hemisphere. The patient was implanted with VNS. After changing VNS parameters (current output of 2.5 mA and ON time of 3.3 sec), his mother started to report recurrent episodes of abnormal nocturnal noises. The patient complained of excessive daytime sleepiness. Video-PSG showed severe mixed apnoea with desaturation (obstructive apnoea index: 8.2/h; central apnoea index: 2.0/h; mixed apnoea index: 13.8/h; with episodes of respiratory distress involving stridor followed by a catathrenia-like sound both in REM and non-REM sleep). In this patient, the catathrenia-like sounds did not occur with prolonged expiration (*figure 2 and audio 4*). The events always occurred during VNS ON time. A drug-induced sleep endoscopy (DISE) performed with midazolam induction, followed by propofol perfusion (to achieve a BIS level between 50 and 70), with concomitant PSG monitoring, was performed. During these procedures, VNS OFF time revealed glossoptosis, "trap door" of the epiglottis, and paresis of the left side of the larynx and ipsilateral vocal cords. During ON time (current output between 1.5 to 2.5 mA), right vocal cord adduction with anterior and posterior collapse of the right side of the larynx were observed (*figure 3B*). PSG monitoring performed during DISE showed,

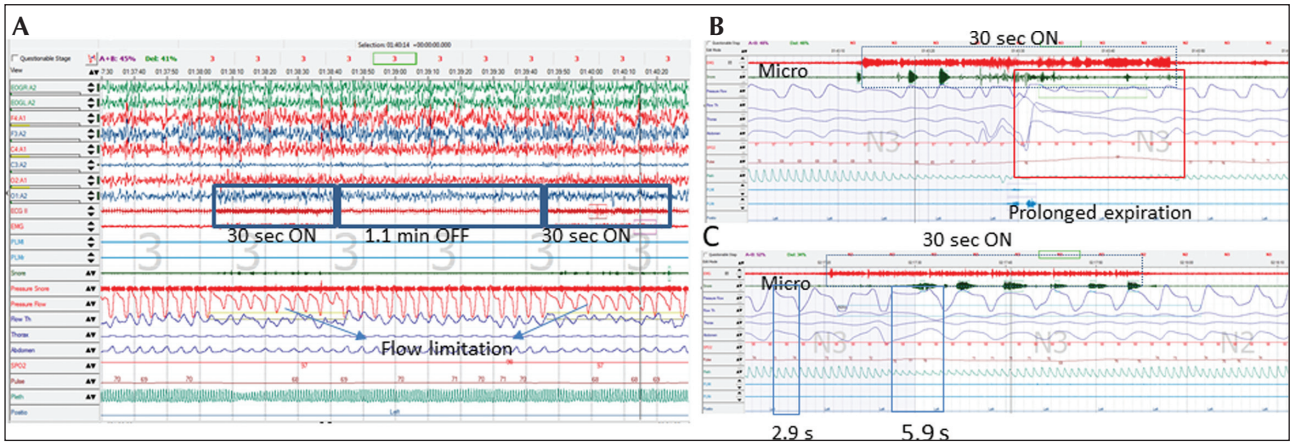

Figure 1. PSG images from Patient 1. (A) Full PSG montage showing the cycling with 30 seconds ON and 1.1 seconds OFF, as indicated by artefact in the EMG channel. During VNS ON time, flow limitation and respiratory sounds are observed. (B) Catathrenia-like episodes during VNS ON time. On the abdominal and thoracic effort channels, a prolonged expiration can be seen, accompanied by sound registered in the microphone channel (*audios 2 and 3*). (C) Catathrenia-like episodes during VNS ON time with less prolonged expiration. Even in these episodes, slightly prolonged expiration, in comparison to pre-VNS ON time, can be seen (events are highlighted in boxes) (*audios 2 and 3*).

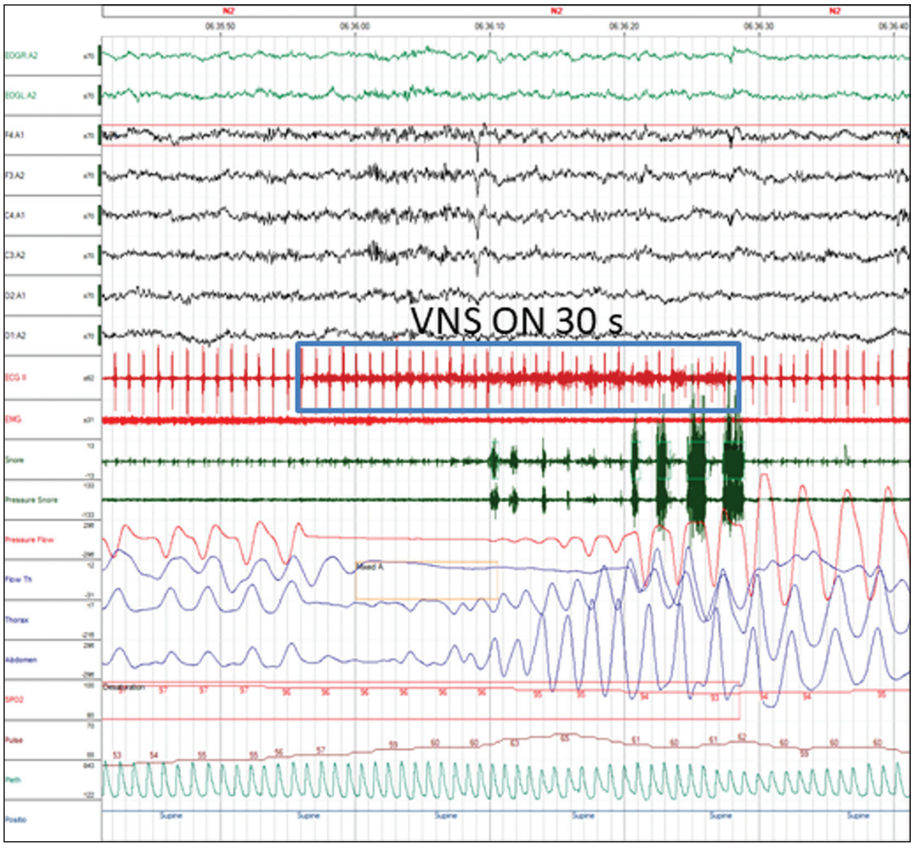

Figure 2. PSG image from Patient 2. The image shows mixed apnoea, time-locked to a 30-second VNS-ON time, as indicated by the artefact in the EMG channel (boxed event). The mixed apnoea is followed by respiratory sounds, first inspiratory stridor, and afterwards an expiratory groaning sound, without prolonged expiration (green: snore channel). All events stop when stimulation subsides.

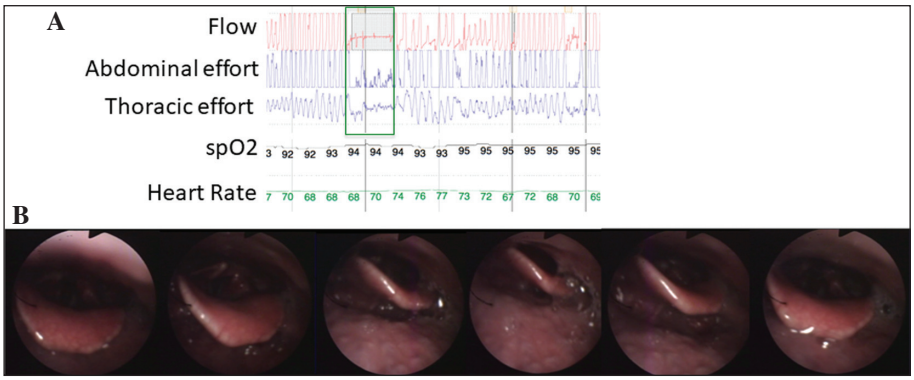

Figure 3. (A) PSG performed during DISE showing a respiratory event during VNS stimulation (1.5-2.5 mA). (B) Photogram showing the accompanying right pharyngeal and epiglottis collapse. The boxed event on the PSG image shows an obstructive apnoea followed by apparent central apnoea. The flow channel shows no ventilation. In the thoracic belt, there are few thoracic movements followed by an absence of effort. The abdominal effort channel shows interference due to artefacts caused by manipulation of the patient during the procedure. During the procedure, no respiratory effort was detected during the apnoea while observing the patient. These events subsided at 1 mA VNS. Despite the apparent central apnoea, DISE showed upper airway obstruction (B).

Table 1. Timing and characteristics of VNS parameters relative to the occurrence and resolution of sleep-related adverse events. Patient 2 improved only partially with CPAP.

Patient	VNS start	Date of AE	VNS settings with AE	AEs	VNS settings to suppress AEs
1	30/12/2010	12/10/2011	CO: 1.75 mA PW: 500 µsec F: 30 Hz 30 sec ON 1.8-1.1 min OFF	Anterior cervical contraction in the larynx region; nocturnal "noises" PSG – snoring, flow limitation and catathrenia-like sounds	CO: 1.25 mA PW: 500 µsec F: 30 Hz 30 sec ON 3 min OFF
2	17/12/2010	3/12/2015	CO: 2.5 mA PW: 250 µsec F: 30 Hz 30 sec ON 1.1 min OFF	Nocturnal "noises" PSG: obstructive sleep apnoea + nocturnal stridor + catathrenia-like sounds	CO: 1.1 mA PW: 250 µsec F: 30 Hz 30 sec ON 1.1 min OFF + CPAP

AE: adverse events: CO: current output; PW: pulse width; F: frequency; PSG: polysomnography.

during these periods of pharyngeal collapse, patterns suggestive of both obstructive and central sleep apnoea. Central apnoea was occasionally preceded by a short period in which the respiratory effort was present, followed by a clear central pattern (*figure 3A*). During this procedure, we could not reproduce the abnormal respiratory sounds. However, when current output was reduced to 1.0 mA, there was only partial resolution of the previous observed findings. Follow-up video-PSG after VNS parameters were changed showed persistent obstructive sleep apnoea (RDI: 29.2/h; ODI: 15.2/h) and rare catathrenia-like sounds, without stridor. Therefore, the patient was also treated with continuous positive airway pressure (CPAP). The patient's sleepiness and nocturnal groaning improved. See *table 1* for a summary of the timing and characteristics of VNS parameters relative to the sleep related adverse events in both patients.

Discussion

SBD have been emerging as a common side effect of VNS treatment in epilepsy patients (Malow *et al*., 2000; Murray *et al*., 2001; Holmes *et al*., 2003; Marzec *et al*., 2003; Khurana *et al*., 2007; Hsieh *et al*., 2008; Parhizgar

et al., 2011). It has been postulated that VNS afferent modulation of dorsal medullary respiratory centres may increase both respiratory effort and airway obstruction during ON time (Malow *et al*., 2000; Holmes *et al*., 2003; Marzec *et al*., 2003; Nagarajan *et al*., 2003; Hsieh *et al*., 2008; Gschliesser *et al*., 2009). More recently, laryngeal motility dysfunction during VNS ON time, in particular left vocal cord adduction, was described by Zambezi and co-workers (Zambrelli *et al*., 2016). These findings support that retrograde stimulation of the vagus nerve efferent fibres, via central medullary pathways, may result in dynamic contraction of the laryngeal adductors during inspiration.

DISE is a technique that involves assessment of individuals under pharmacologic sedation, designated to stimulate natural sleep, utilizing fiberoptic endoscopy to examine dynamic upper airway collapse during sleep (Chong *et al*., 2019). It may be a valuable clinical tool to investigate VNS laryngeal complaints and vocal cord findings in epileptic patients (Zambrelli *et al*., 2016). Actually, DISE may help to better clarify the subjacent mechanisms between sleep disorders and VNS (Zambrelli *et al*., 2016). In our second patient, the DISE procedure was crucial for monitoring the effect of multiple VNS parameter changes on respiration and laryngeal side effects.

Our cases demonstrate that other sleep disorders, such as stridor and catathrenia, may also be a complication of VNS treatment. Stridor, as a side effect of VNS therapy, has been already reported in two adults (Bhatt *et al*., 2010; St Louis and Faber, 2010) and two paediatric (Kelts *et al*., 2015) epileptic patients, and its resolution was seen in all patients following adjustment of VNS settings. Nonetheless, to the best of our knowledge, VNS-induced catathrenia has not previously been described. Catathrenia is a rare and poorly understood sleep-related respiratory condition, whose clinical features include loud-vocal groaning sounds and markedly prolonged expiration. They occur mainly, but not exclusively, in REM sleep (Drakatos *et al*., 2017; Pevernagie, 2017). Its precise epidemiology remains unknown. Patients are often unaware of their sleep-related groaning, which is usually noted by their bed partner or a family member (Ott *et al*., 2011; Drakatos *et al*., 2017), as was the case in both our patients. This phenomenon is not associated with abnormal motor activity or other parasomnias. In our patients, the nocturnal groaning observed was slightly different from that reported in the literature. In the first patient, there was a groaning-like sound accompanied by increased expiratory time, but this never lasted more than five seconds. In the second patient, only the abnormal sound was detected, without concomitant bradypnea. Physical examination, including direct laryngoscopy during wakefulness, is usually unremarkable (Ott *et al*., 2011; Drakatos *et al*., 2017; Pevernagie, 2017). Ott *et al*. described, for the first time, catathrenia during DISE in a 29-year-old patient, and the authors showed active adduction of the vocal cords followed by a vibration during expiration, in a similar way to normal phonation (Ott *et al*., 2011). Our second patient was referred for DISE, but no episodes suggestive of a catathrenia-like sound were recorded, probably due to their intermittent nature and preponderance in REM sleep, which rarely occurs during this procedure. However, the observed laryngeal motility dysfunction during ON time in both patients supports a similar mechanism for the production of this abnormal sound. The complete mechanism for spontaneous catathrenia is possibly different from that triggered by VNS, as very prolonged expiration was never observed in our patients and the events were recorded in non-REM sleep.

Several studies have shown that modifying VNS parameters, namely increasing OFF time or decreasing stimulation intensity, may be effective in resolving SBD symptoms (Malow *et al*., 2000; Marzec *et al*., 2003; Parhizgar *et al*., 2011; Bhat *et al*., 2012; Zambrelli *et al*., 2016). Moreover, previous studies have confirmed that CPAP treatment may be successful in some patients with VNS-induced SBD (Holmes *et al*., 2003; Hsieh *et al*., 2008; Parhizgar *et al*., 2011; Zambrelli *et al*., 2016). It has also been suggested that VNS setting adjustment may further enhance the impact of CPAP (Ebben *et al*., 2008). Indeed, in our second patient, besides altering VNS parameters, concomitant CPAP treatment was needed to significantly improve his symptoms. This was detected during the DISE procedure, anticipating the need to adapt a CPAP machine.

Another interesting finding from our second patient concerns the observed central sleep apnoea pattern. Central sleep apnoea has been previously described as a possible side effect of VNS (Papacostas *et al*., 2007; Zambrelli *et al*., 2016; Forde *et al*., 2017). In our second case, however, we demonstrated that some of this apparent central sleep apnoea is in fact associated with or preceded by a laryngeal collapse, perhaps as a result of reduced central drive to upper airway dilator muscles (Hernandez and Patil, 2016). Therefore, it seems reasonable that in some patients with VNS and central sleep apnoea, the mechanism may also be laryngeal occlusion. DISE may be considered to study these patients, especially if refractory to VNS parameter changes.

In conclusion, our case studies broaden our knowledge about sleep disorders related to VNS, particularly stridor and catathrenia. Furthermore, we suggest that central sleep apnoea induced by VNS may be associated with laryngeal occlusion and that DISE may be considered in selected cases as a valuable clinical tool to evaluate, in a single session, the effectiveness of multiple VNS parameter changes on respiration and laryngeal side effects. □

Legend for video sequences

Video sequence 1

Laryngoscopy during wakefulness and VNS ON time. A left vocal cord and laryngeal bascule can be observed.

Video sequence 2

Laryngoscopy during wakefulness and VNS OFF time. Subtle left vocal cord paresis can be observed.

Key words for video research on www.epilepticdisorders.com

Phenomenology: apnoea, stridor
Localisation: vagus nerve
Syndrome: sleep-disordered breathing
Aetiology: vagus nerve stimulation (VNS)

Supplementary data.
Summary didactic slides and audios are available on the www.epilepticdisorders.com website.

Audios 1, 2 and 3 were recorded during the PSG. All episodes were recorded during VNS ON time. Audio 1 shows snoring. Audio 2 shows repetitive expiratory groaning episodes during VNS ON time. The first is slightly more prolonged and lasts around four seconds. Audio 3 shows brief expiratory sounds resembling groaning, despite being very brief and without prolonged expiration. The sounds are more vocal and harmonic than the usual snore. These sounds recur at every expiration for around 33 seconds and then subside.
Audio 4 was recorded during an episode of stridor and catathrenia-like sound during the video-PSG of Patient 2. The beginning of the audio corresponds to the apnoea, followed by stridor sounds and then expiratory groaning. The entire episode lasts around 30 seconds, during VNS ON time.

Disclosures.
None of the authors have any conflicts of interest to declare.

References

Chong KB, De Vito A, Vicini C. Drug-induced sleep endoscopy in treatment options selection. *Sleep Med Clin* 2019; 14: 33-40.

Bhat S, Lysenko L, Neiman ES, Rao GK, Chokroverty S. Increasing off time improves sleep-disordered breathing induced by vagal nerve stimulation. *Epileptic Disord* 2012; 14: 432-7.

Bhatt YM, Hans PS, Belloso A. Airway compromise secondary to vagus nerve stimulator: case report and implications for otolaryngologists. *J Laryngol Otol* 2020; 124: 557-9.

Drakatos P, Higgins S, Duncan I, *et al*. Catathrenia, a REM predominant disorder of arousal? *Sleep Med* 2017; 32: 222-6.

Ebben MR, Sethi NK, Conte M, Pollak CP, Labar D. Vagus nerve stimulation, sleep apnea, and CPAP titration. *J Clin Sleep Med* 2008; 4: 471-3.

Forde IC, Mansukhani MP, Kolla BP, Kotagal S. A potential novel mechanism for vagus nerve stimulator-related central sleep apnea. *Children (Basel)* 2017; 4.

Gschliesser V, Hogl B, Frauscher B, Brandauer E, Poewe W, Luef G. Mode of vagus nerve stimulation differentially affects sleep related breathing in patients with epilepsy. *Seizure* 2009; 18: 339-42.

Hernandez AB, Patil SP. Pathophysiology of central sleep apneas. *Sleep Breath* 2016; 20: 467-82.

Holmes MD, Chang M, Kapur V. Sleep apnea and excessive daytime somnolence induced by vagal nerve stimulation. *Neurology* 2003; 61: 1126-9.

Hsieh T, Chen M, Mcafee A, Kifle Y. Sleep-related breathing disorder in children with vagal nerve stimulators. *Pediatr Neurol* 2008; 38: 99-103.

Kelts G, O'Connor PD, Hussey RW, Maturo S. An electrical cause of stridor: pediatric vagal nerve stimulators. *Int J Pediatr Otorhinolaryngol* 2015; 79: 251-3.

Khurana DS, Reumann M, Hobdell EF, *et al*. Vagus nerve stimulation in children with refractory epilepsy: unusual complications and relationship to sleep-disordered breathing. *Childs Nerv Sys* 2007; 23: 1309-12.

Malow BA, Edwards J, Marzec M, Sagher O, Fromes G. Effects of vagus nerve stimulation on respiration during sleep: a pilot study. *Neurology* 2000; 55: 1450-4.

Marzec M, Edwards J, Sagher O, Fromes G, Malow BA. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. *Epilepsia* 2003; 44: 930-5.

Murray BJ, Matheson JK, Scammell TE. Effects of vagus nerve stimulation on respiration during sleep. *Neurology* 2001; 57: 1523-4.

Nagarajan L, Walsh P, Gregory P, Stick S, Maul J, Ghosh S. Respiratory pattern changes in sleep in children on vagal nerve stimulation for refractory epilepsy. *Can J Neurol Sci* 2003; 30: 224-7.

Ott SR, Hamacher J, Seifert E. Bringing light to the sirens of night: laryngoscopy in catathrenia during sleep. *Eur Respir J* 2011; 37: 1288-9.

Papacostas SS, Myrianthopoulou P, Dietis A, Papathanasiou ES. Induction of central-type sleep apnea by vagus nerve stimulation. *Electromyogr Clin Neurophysiol* 2007; 47: 61-3.

Parhizgar F, Nugent K, Raj R. Obstructive sleep apnea and respiratory complications associated with vagus nerve stimulators. *J Clin Sleep Med* 2011; 7: 401-7.

Pevernagie DA. Why catathrenia is a parasomnia. *Sleep Med* 2017; 32: 227-8.

St Louis EK, Faber K. Reversible sleep-related stridor during vagus nerve stimulation. *Epileptic Disord* 2010; 12: 76-80.

Zambrelli E, Saibene AM, Furia F, *et al*. Laryngeal motility alteration: a missing link between sleep apnea and vagus nerve stimulation for epilepsy. *Epilepsia* 2016; 57: e24-7.

TEST YOURSELF

(1) Which side effects are related to vagus nerve stimulation (VNS)?

(2) Why was drug-induced sleep endoscopy (DISE) so useful in the management of sleep disorders after VNS in the second patient?

(3) How was complex sleep-disordered breathing, after VNS, treated in both patients?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".