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Bi-level VNS therapy with different therapy modes at night and daytime improves seizures and quality of life in a patient with drug-resistant epilepsy

Berthold R. Voges

Protestant Hospital Hamburg-Alsterdorf, Dpt. of Epileptology, Elisabeth-Flügge-Str.1, 22337 Hamburg, Germany

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ABSTRACT

Induction or aggravation of sleep apnea is a known side effect of vagus nerve stimulation (VNS). We report the case of a 44 year old male with drug-resistant epilepsy and depression who did not experience any seizure reduction after 1 year of VNS but a worsening of depression and daytime sleepiness. After confirming VNS-associated sleep apnea we started the first bi-level VNS therapy with standard VNS settings during daytime and reduced settings during nighttime. Anti-seizure medication remained unchanged. Within 12 months his seizure frequency was reduced by 90 % and his depression improved, permitting a cessation of his antidepressant medication. The observations made in this case have contributed to the manufacturer of VNS developing new generator models that can automatically provide bi-level VNS.

Introduction

Induction or aggravation of sleep apnea is a known side effect of vagus nerve stimulation (VNS) [1–5] and is considered to be due to innervation of the left recurrent nerve and the superior laryngeal nerve which are both branches of the vagus nerve. This leads to tonic contraction of their motor supply areas in the pharynx and at the left vocal cord resulting in restriction of the airways during VNS on phases, which can be visualized laryngoscopically [5]. Attempts to treat VNS-induced apneas with protrusion splint of lower jaw have not been reported to date and attempts to treat them with CPAP are often not effective [6] due to the different pathomechanism behind VNS associated apneas: CPAP is suitable to treat obstructive apneas, produced by collapse of the hypotonic wall of the soft palate during inspiration, however CPAP is not effective in treating restrictive apneas like those induced by an excessive tonic contraction of the pharynx during VNS activation.

Due to these side effects on respiration, VNS therapy has the potential to aggravate a very frequent comorbidity of epilepsy: in patients with refractory epilepsy, mild to severe obstructive sleep apnea (OSA) was reported in one third of patients [7]. These findings have been confirmed by later studies identifying an OSA prevalence of 30 % in 130 patients with unselected epilepsy severity [8] and moderate to severe sleep-disordered breathing in 26 % of 370 consecutive patients with epilepsy and/or PNES admitted for inpatient video-EEG monitoring [9].

In numerous retrospective and prospective evaluations, OSA has been shown to be correlated with cognitive impairment, dementia and depression [10–16]. Treating OSA with CPAP therapy has been shown to lead to improvement of executive function [17] and depressive symptoms [18,19]. These effects are so strong, that CPAP has been proposed as first line therapy in patients with OSA and depression, before starting a pharmacological treatment [18].

With a prevalence of approximately 60 %, mood disorders are an even more common comorbidity in drug resistant epilepsy. (DRE) [20]. Since VNS therapy is effective [21,22] and FDA-/EMA-approved for the adjunctive treatment of both drug resistant epilepsy and depression [23–25], the presence of depression in a patient with DRE may be an argument for opting for VNS therapy when resective epilepsy surgery is not possible or has failed. However, as described above, VNS can induce or aggravate OSA, and by this potentially trigger depressive symptoms and antagonize its own antidepressant effects.

Sleep fragmentation due to OSA may also worsen seizures and by this antagonize the anti seizure effects of anti-seizure therapies [26,27]. Treating the underlying sleep disturbing pathology may result in better seizure control as has been demonstrated for CPAP which resulted in improved seizure control in patients with epilepsy and sleep apnea [28,29].

Also other factors with negative effects on sleep may lead to a

E-mail address: b.voges@alsterdorf.de.

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worsening of day time vigilance, mood and seizure burden, such as frequent sleep related seizures, somnological diseases such as restless legs syndrome or anticonvulsant therapies with sleep-disturbing side effects. In patients with DRE treated with adjunctive deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) we found dose-dependent sleep fragmentation by the stimulations [30,31]. After reducing ANT-DBS voltage overnight we observed rapid improvement in affective and cognitive side effects of ANT-DBS without hampering efficacy and in later follow-up reduced seizure frequency.

In the present case, we were confronted with a patient suffering from DRE and depression taking three anti-seizure medications (ASMs) in addition to VNS therapy. After one year of VNS therapy he did not experience any seizure reduction but instead to a worsening of depression and daytime sleepiness.

Material and methods

History

A 44 year old male with drug-resistant focal epilepsy since age 16 is the subject of this report. The epilepsy was of unknown origin, his seizures were characterized by focal aware tonic seizures (with toning in the face and left or right arm, head turning -sometimes to the left, sometimes to the right; frequency unclear due to contradictory information), focal impaired awareness tonic seizures and focal impaired awareness automatism seizures (3 – 8 seizures per month) and focal impaired awareness tonic seizures with rapid (seconds) transition to bilateral tonic-clonic seizures (2 – 3 seizures per month). By age 44 the patient had been treated with 11 ASMs (*drug/documented maximum dose* / documented maximum serum level): *phenobarbital / no documented maximum dose* / documented maximum serum level 19 mg/l; *phenytoin 350 mg*/unknown, *valproate 3000 mg*/106 mg/l, free VPA15mg/l; *topiramate 400 mg*/unknown; *carbamazepine 400 mg/* 8 mg/l; *oxcarbazepine 2100 mg* /unknown, *levetiracetam 2000 mg*/unknown; *lamotrigine 800 mg/* 9 mg/l; *lacosamide 500 mg/* 10 mg/l; *zonisamide 500/* 24 mg/l; *perampanel 14 mg /* 632 mg/l). All ASMs had been given in high dosages. All had obtained adequate serum levels during close monitoring of drug levels, so ASM adherence was not considered to be a problem. ASMs failed to achieve seizure-freedom or at least a tolerable seizure situation.

The patient was obese (174 cm, 102 kg, BMI 33,7) and suffered from impulse control disorder and major depressive disorder with anxiety for which he took antidepressant and neuroleptic medication for at least 15 years: Amitriptyline 50 mg, flupentixol depot all 2 weeks in unknown maximal dosage, trimipramin 200 mg, lorazepam 2 mg, citalopram 20 mg and olanzapine 17,5 mg. Neither the treating psychiatrists nor we had any doubts about adherence to his antidepressants or anxiolytics, however their serum levels had not been monitored. Furthermore, already at his first presentations to our hospital, at age 29, the patient had reported gender dysphoria since age 15, with the feeling of being born in the wrong body.

Diagnostic findings

Between 1987 and 2000 the patient was treated in another German epilepsy center with the following diagnostic findings: In numerous short-term EEG and at least two times Video-EEG-monitoring (VEM) examinations multiregional interictal epileptiform discharges (IED) both left frontal or frontotemporal and right frontal or frontotemporal were reported. One bilateral tonic-clonic seizure had been recorded under EEG with diffuse generalized theta rhythm. When attempting ictal SPECT only a postictal SPECT could be obtained, with slight right temporal hypoperfusion. Several examinations of MRI and cerebrospinal fluid (CSF) showed no abnormalities. Between 2000 and 2016 we saw him 8 times as an outpatient and treated him as an inpatient 9 times, for a total of 35 weeks. Over these years five additional VEM examinations were performed which found right and left frontal (electrodes in the 10–20 scheme: F4 > Fp2,C4 or Fp1, F3 > C3,P3) or frontotemporal (max F8,T4 or F7,T3) but also right or left frontoparietal IED (Max C4,P4,T6 or C3,P3,F3). In addition we found also paroxysms of generalized 2–4/s spike wave activity. We were unable to record a seizure under EEG. However one to six bilateral tonic-clonic seizures (BTCS) were documented on video monitoring during each hospital stay, often accompanied by serious injuries (e.g. fractures of the thorax, vertebrae, midface, of jaw or nose). The situation was further complicated by the fact that psychogenic non-epileptic seizures, with a semiology of trembling, shaking and stuttering, clearly distinguishable from BTCS were recorded. We repeated MRI together with post processing several times, as well as CSF diagnostics and searched for autoimmune antibodies. All examinations were negative. Neuropsychological examination corroborated executive and unspecific mnestic deficits. We discussed the possibility of invasive EEG monitoring, but also the need for an extensive exploration with implantation of electrodes bilaterally in frontal, temporal and parietal lobes. This was not desired by the patient, who at that point ruled out epilepsy surgery. Given the inconsistent data situation and the multi-regional EEG abnormalities, we did not conduct an interictal PET nor a MEG investigation and we did not insist on further presurgical evaluation.

Therefore he was implanted with a vagus nerve stimulator (VNS Therapy Model 106 (AspireSR™), LivaNova PLC, London). Because the patient displayed noticeable ictal tachycardia in more than half of his seizures, cardiac based seizure detection was enabled in his VNS generator in order to provide responsive VNS Therapy.

Effect of standard VNS therapy (April 2015 – April 2016)

A VNS Therapy System (LivaNova PLC) was implanted in April 2015. During the 12 months before implantation, the medication was stable with perampanel 14 mg/d (started in 2013, serum level at VNS implantation 490 mg/l), lacosamide 400 mg/d (started in 2013, serum level at implantation 7,5 mg/l) and lamotrigine 200 mg/d (restarted in 2013, serum level at implantation 5 mg/l), citalopram 20 mg started in 2013) and olanzapine 17,5 mg/d (started in 2011). In September 2015, 5 months after VNS implantation we reduced perampanel from 14 to 12 mg/d, in order to return to the highest dosage of that drug approved in Germany as exceeding the maximum dose had not provided any additional benefit. After 7 months of VNS (normal mode: 1,875 mA (maximum tolerated dose), frequency 20 Hz, pulse width 250 us, On-Time: 30 s, Off-Time 5 min; magnetstimulation: 2 mA, 60 s; autostimulation: 2 mA, 60 s; seizure-detection-heart-rate-threshold 40 %); only a 20 % seizure frequency reduction was achieved, leading to the classification of the patient as a VNS-non-responder. Therefore topiramate 100 mg/d was added. However we stopped it some weeks later due to side effects and BTCS persistence and after getting the information that the patient had already unsuccessfully taken topiramate up to 400 mg in the first years of his epilepsy. At the beginning of March 2016 perampanel was stopped and brivaracetam 200 mg added, despite knowing that levetiracetam 2000 mg/d had been ineffective before, due to the fact that the patient seemed to be a VNS non-responder, with persistence of very frequent (at that time 3–4) injury-causing BTCS per month. However, during the following 4 weeks of inpatient treatment under video monitoring, increased seizure-frequency despite brivaracetam add-on therapy was observed.

After 12 months of VNS there still was no seizure reduction, however depression and anxiety had worsened and the patient reported headaches in the morning as well as daytime sleepiness.

Polysomnographic evaluation of sleep-related comorbidities before VNS and with standard VNS therapy

After 12 months of standard VNS therapy we admitted the patient to our VEM to evaluate whether sleep fragmentation due to VNS may be occurring. Three years prior, the overweight patient already underwent

extensive VEM diagnostics, together with cardiorespiratory polysomnography (PSG) revealing mild sleep apnea with an apnea-hypopnea index (AHI) of 9/h and O2 basic 97 %, mean desaturation 93 %, max desaturation 80 %, time spent with O2 < 90 %: 9 min. In this current second VEM admission with PSG we placed additional electrodes around the neck scar where the VNS electrode is wrapped around the vagus nerve. This allows for detection of the stimulation phases of the VNS device and therefore a correlation with events like seizures or sleep-related events like apneas or arousals.

We detected frequent apneas associated with VNS stimulation phases, often leading to arousal or awakening of the patient (see Fig. 1). We observed a severe sleep-apnea syndrome (21 apneas/hypopneas per hour, most of them correlated with arousals; max. O2: 98 %, mean O2 desaturation: 85 %, max. O2 desaturation: 72 %; total time with O2 < 82 %: 01h04min, total time with O2 < 79 %: 23 min) together with strong sleep fragmentation (sleep efficiency: 79 %, 43 wake-times, wake after sleep-onset: 1,7h; see Fig. 2).

In our patient VNS was well tolerated during daytime but caused clinically relevant side effects during sleep which the patient did not realize themselves but only indirectly by the consequences: aggravation of seizures and depression and daytime sleepiness.

Reducing VNS strength overnight – A way out of the therapeutic dilemma?

We hypothesized that potential therapeutic effects of VNS (improvement of seizures, antidepressant effects) may have been antagonized by sleep-related negative side effects of VNS and therefore, that reducing VNS intensity during the nighttime may represent a solution. Literature on the adequate settings to avoid induction or aggravation of sleep-related breathing disorders by VNS is limited, Therefore we used the scarce literature available at that time [32,33], and our previous experience with bilevel ANT-DBS established 2 years prior, as mentioned above [30]. In that patient group, reduction of ANT-DBS output overnight by approximately 30 % −50 % of daytime therapy strength had resulted in good control of DBS-induced sleep fragmentation. Therefore, we adopted the extent of nocturnal output reduction also for bilevel VNS, despite very different mechanisms being involved in the sleep-disrupting mechanisms of ANT-DBS and VNS.

In April 2016, 13 months after implantation of VNS, we started - to our knowledge for the first time worldwide – bilevel - VNS with standard settings during the day but lower output currents (OC) and shorter On–Times at night. At that time, there was no possibility to program different stimulation programs depending on the time of day, with automatic switching between those programs. For this, we supplied the patient with a VNS programming device (M250 LivaNova PLC, London

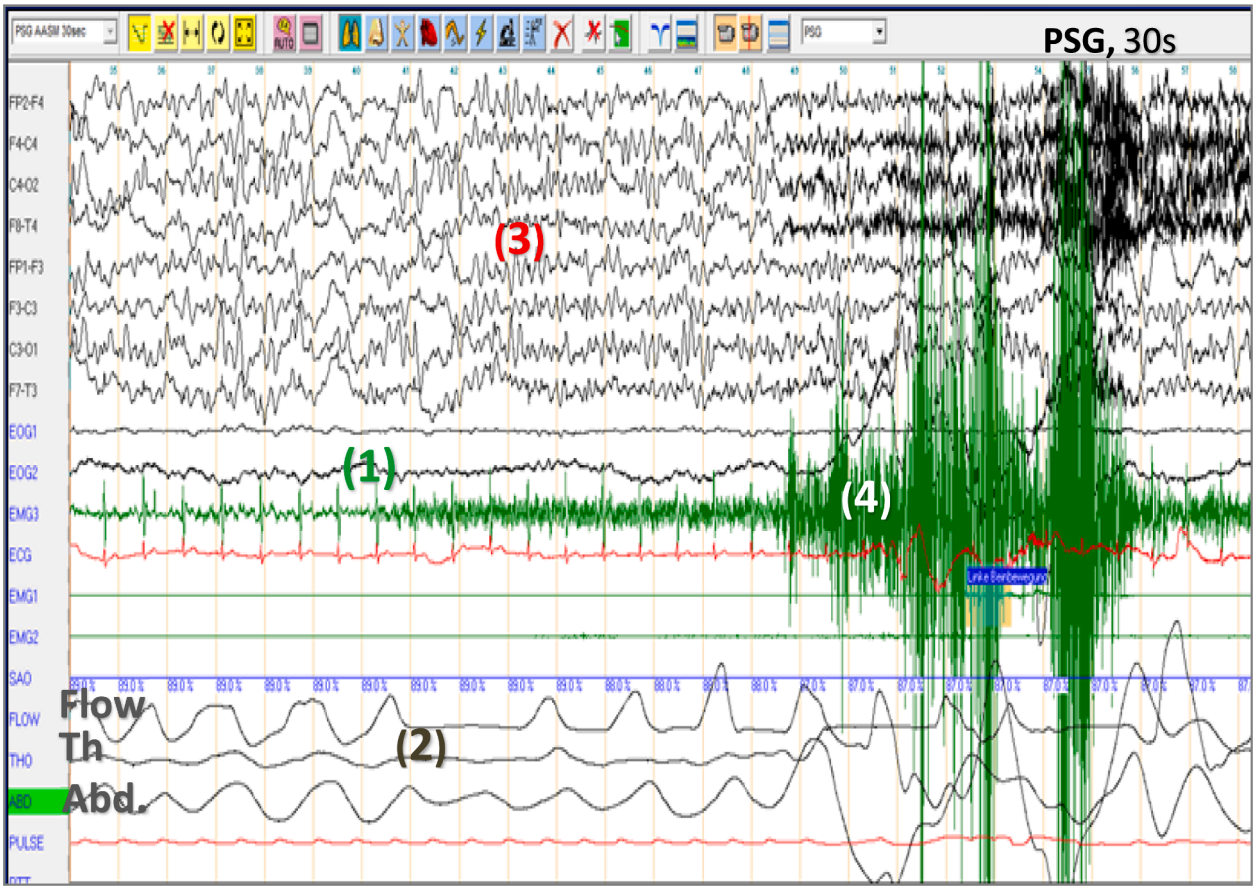

Fig. 1. Example of a VNS-induced respiratory event leading to awakening, in our patient with lack of VNS efficacy and impairment of mood and daytime sleepiness 1 year after starting a standard VNS therapy: Timescale 1 page = 30 sec.; polysomnography (PSG) with – from above - EEG (bipolar lines, amplitude 7 uV/ mm, low frequency filter 0,3 Hz, high frequency filter 70 Hz); EOG 1 + 2: Electrooculogram for detection of eye movements; EMG 3: supplementary channel for detection of VNS activity (marked in green) with collection of signal by additional electrode at neck, above insertion of the VNS lead at vagus nerve; ECG (marked in red); EMG 1+2 of both Tibialis anterior muscles (marked in green); Oxygen saturation (marked in blue); nasal flow; respiratory excursions of thorax and abdomen (marked in black), pulse wave (marked in red). 2 s after the onset of the VNS impulse (1), a respiratory event begins with stop in the nasal airflow, then reduced and antidromic movements of thorax and abdomen (2), some seconds later awakening of the patient with alpha rhythm in EEG (3) and violent coughing with strong movement artefact in green channel for VNS-signals (4). At the beginning of this example, O2 is already low (89 %) due to the frequent apneas and hypopneas that occurred before this respiratory event (21 apneas and hypopneas / h). The patient is quickly awakened by the VNS and by hypopnea and coughing, so that there is no further oxygen desaturation in this example.

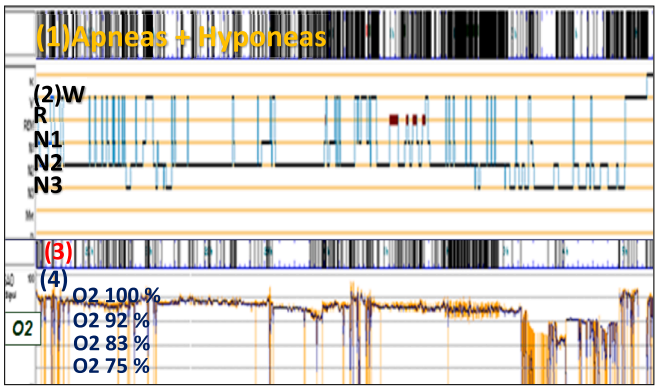

Fig. 2. Hypnogram of the same night as in Fig. 1, with detection of strong sleep fragmentation together with a severe sleep-apnea syndrome, most of them correlated with arousals: In the top line summation of respiratory events (1); in the line below, the hypnogram after scoring into the different wake-sleep stages W, N1, N2, N3 and R (2) showing a severe sleep fragmentation with many arousals (alpha EEG 3–15 sec), awakenings (arousal with clinical awakening) and wake-times (alpha EEG > 15 sec), resulting in poor sleep efficiency (79 %), 43 wake-times and a wake after sleep-onset time of 1,7h. Sleep fragmentation was induced by VNS-related respiratory events (21 apneas/hypopneas per hour; frequent coughing attacks). In the third line (3) summation of apneas/hypopneas coming together with arousals, waking up or cough attacks, at the bottom line (4) the visualization of O2 desaturations (max O2: 98 %, mean O2: desaturation 85 %, max. O2 desaturation: 72 %; total time with O2 < 82 %: 01 h 04 min; O2 < 79 %: 00 h23 min).

UK) and taught him how to use it. This allowed him to – as instructed by us - manually program the normal mode and autostimulation OCs to 1.75 mA and the autostimulation On– time to 60 s upon waking up in the morning. Before going to sleep he would program the normal mode OC to 1 mA, autostimulation OC to 0.5 mA and autostimulation On-time to 30 s. Frequency, pulse-width and normal mode On-time remained at 20 Hz, 250 μsec and 30 s respectively in both modes. Upon initiating bilevel VNS the patient was undergoing ASM treatment with brivaracetam 200 mg/d, lamotrigine 200 mg/d (serum level 5–6 mg/l) and lacosamide 400 mg/d (SL 5,5–7 mg/l).

Results

Outcome of the bilevel VNS therapy in this patient, effects on seizures, mood and quality of life (April 2016 – 2023)

After the start of VNS bilevel therapy his anti-seizure medication remained unchanged for the following 5 years, as did their serum levels (measured for lamotrigine and lacosamide). Citalopram was tapered off at the beginning of 2017. Hormonal therapy started in May 2017 to address gender dysphoria. Olanzapin was reduced and temporarily discontinued, but reintroduced with 10 mg in 2021. Following the patient‘s request lacosamide was reduced to 300 mg/d in 2022, since the seizure situation was stable.

Just a few days after changing the therapy regimen, the patient reported much better sleep quality. Three, four and six months after initiating bilevel VNS seizure frequency decreased by 30 %, 50 % and 70 % respectively. After 1 year of bilevel VNS the patient‘s seizure frequency was reduced by more than 90 % with a decrease in BTCS from 2 to 4 per month to 1 approximately every 6 months and finally up to now, 7 years later - to 1–2 BTCS per year. Focal aware tonic seizures, focal impaired awareness tonic seizures and focal impaired awareness automatism seizures were not reported anymore, neither by the patient, nor by persons around him. After onset of bilevel therapy with VNS there had been for the following 5 years, and up to date, no more fractures, no seizure-related emergency interventions and no seizure-related hospitalizations. In addition, also his psychogenic seizures ceased. Both his depression and anxiety disorder improved. It became possible to halve neuroleptic and to stop antidepressant medication, which he had been taking for 15 years. The formerly obese patient experienced a weight loss of 30 kg and started to train for a marathon. By the patient‘s own account, improvement of both his seizure and mood disorder “gave him the strength to do what he had wanted to since age 15”: undergo gender reassignment surgery. After successful gender reassignment to female the patient changed his/her name and is now legally a woman. We offered the patient another polysomnographic evaluation in our sleep lab, in order to confirm the successful treatment of her VNS-induced sleep-apnea. However, she declined to come back as an in-patient stating that now with her epilepsy and depression being under control she has started “a new life”. The follow up of her epilepsy continues as a regular outpatient to this day.

Discussion

30 % of patients with drug-refractory epilepsy suffer from sleep apnea, so they are at a higher risk for sleep-disordered breathing than the normal population [7–9]. The consequences of apneas can be sleep fragmentation and chronic sleep deprivation which may lead to aggravation of epileptic seizures. Therefore, successful treatment of a coexisting sleep-related breathing disorder may be a prerequisite for successful treatment of epileptic seizures [9,26–29].

Induction or aggravation of sleep apnea is a well-known side effect of VNS [1–5]. By this, induction or aggravation of a sleep-related breathing disorder by VNS might antagonize the potential therapeutic effect of VNS on epilepsy and also on depression

In our epilepsy center, we treat approximately 250 patients with VNS therapy. In our patients with conventional VNS therapy systems, without additional autostimulation, we suspect induction of new-onset daytime sleepiness, snoring or apneas in about 5 % of patients based on clinical information provided by the patients themselves or their partners. In our patients using VNS Therapy with autostimulation, symptoms of sleep disordered breathing are reported more frequently, in up to approximately 10 % of these patients, however this has not been assessed systematically.

Responsive VNS uses rapid and steep increases of heart rate as a biomarker of seizures in order to trigger an additional stimulation train aimed at interrupting the seizure [34]. Because sudden heart rate accelerations during sleep can also be induced by heavy snoring or apneas, autostimulations may be triggered and - especially if programmed to last not 30 but 60 s – may prolong or aggravate pre-existing apneas, leading to a vicious cycle: More apneas may lead to stronger fragmentation of sleep, which may induce an aggravation of seizures and induce also an impairment of a comorbid depression. An increase in sleep-related seizures, and also an aggravation of depression may result in an even more severe sleep fragmentation, which provokes further aggravation of both seizures and depressive symptoms [35].

Reducing VNS output current overnight may have been the reason for the cessation of the nocturnal sleep disorder in our patient and by this, we think that we might have been able to break the vicious circle described above. Restoring sleep quality may have provided the situation in which VNS is able to exert its anticonvulsant and antidepressant effects.

Other factors with potential influence on the patient́s good clinical development need to be discussed: About 6 weeks before starting bilevel VNS therapy we changed the anti-seizure medication by switching from perampanel to brivaracetam. Usually, the effect of brivaracetam comes quickly, within the first days of therapy. However, we found no effect on seizures during the following 3 months. Seizure reduction began after 8 weeks of bilevel VNS therapy, with progressive further improvement over the following 9 months. Such a clinical course is often seen in epileptological neurostimulation. In addition, levetiracetam 2000 mg/d, used a few years earlier had been without any positive effects, and the mode of action of both brivaracetam and levetiracetam are very similar.

Adding brivaracetam to the antiseizure medication had been an act of desperation, due to the high frequency of BTCS and seizure-related injuries at that time, and we were not surprised, when we found no effect on seizures during the following 3 months. Perampanel has well-known negative psychiatric side effects and taking perampanel out may improve mood of affected patients. However this patient suffered from impulse control disorder and major depression already long before perampanel was introduced in his medication. The severity of his psychiatric symptoms had not changed under perampanel, therefore it seems unlikely that removing perampanel explained the improvement in his depression. Finally, significant weight loss, improvement in sleep and a newly initiated exercise regimen can result in improved seizure control. Better sleep, better mood, better physical conditions and better seizure control can be regarded as interdependent and therefore differentiating between cause and effect is often not possible. In this patient our interpretation of the documented events is that bilevel VNS therapy no longer induced OSAs leading to restored sleep quality which allowed for antidepressant effects of VNS to occur, which motivated the patient to initiate an exercise regimen and lose weight. The weight loss occurred slowly over the course of several weeks, he had no influence on serum levels of the anti-seizure medication and he coincided in time with the appearance of the anticonvulsant effects of VNS. We cannot differentiate whether the obviously VNS-induced improvement of depression was the cause of the seizure reduction, or the direct anticonvulsant effect of VNS. In both cases, it seemed to be the combination of VNS therapy and restoring good sleep quality that brought finally success.

For this reason, we suggest that bilevel VNS may be suitable stimulation paradigm for patients who experience VNS associated sleep-related breathing disorders allowing them to fully benefit from both the anti-epileptic and anti-depressant effects of responsive VNS.

Meanwhile the observations made in this case have contributed to the manufacturer of The VNS Therapy System™ developing new generator models that can automatically provide bi-level VNS without the patient having to manually program the alternating settings (VNS Therapy Model 1000, (SenTiva™) LivaNova PLC, London UK).

Conclusion

In epilepsy patients suffering from VNS-associated sleep apnea or sleep fragmentation, bilevel VNS with reduced output current and/or reduced stimulation on times may offer a solution to the therapeutic dilemma that potential therapeutic effects of VNS (improvement of seizures, antidepressant effects) may be antagonized by sleep-related side effects of VNS. Quantitative dose–response relationships between VNS stimulation parameters and VNS-associated sleep-disturbances must be established to inform prospective investigations of these settings in bilevel VNS therapy in large cohorts.

Ethical statement

This work was neither a study nor an experiment but the result of clinical diagnostic work and clinical treatment in a human patient with approved therapy methods (device and drugs). Only the programming of the device was unusual and was done in a novel way. The patient was informed that the programming of the device was done in a novel way. He gave his consent to this. In addition, he carried out this new programming by himself, after having been instructed how to do it.

He gave his informed consent for publishing his case, the nature and the way of the applied therapy and the resulting outcomes with this case.

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aims for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender are used correctly.

Informed consent was obtained for applying the new therapy mode in this human subject. The privacy rights of human subjects have always been observed.

The personal details of the patient included in the article and in any supplementary materials (including all illustrations) have been removed before submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclosure statement

Berthold R. Voges did not receive any payment or services from a third party for any aspect of the submitted work. Outside the submitted work, Berthold Voges has been reimbursed travel expenses and has received fees for lectures and for the organization of symposias during the past 48 months by Medtronic, LivaNova, UCB, Eisai, Bioprojet, Angelini, GW and Desitin. In addition he has received fees as a consultant for LivaNova. There are no relevant conflicts of interests with the submitted work.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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