Case Report

Pilot data on responsive epilepsy neurostimulation, measures of sleep apnea and continuous glucose measurements

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Abstract

Objectives: To match responsive neurostimulator (RNS) and polysomnographic data to determine if RNS detections and stimulations correlate with measurements of sleep disordered breathing and continuous glucose measurements (CGM).

Materials and methods: In a patient with an RNS with detection/stimulation leads implanted bi-temporally, detection-stimulation counts were matched by time with coinciding polysomnogram and CGM data.

Results: Temporal dispersion of RNS DSC were independent of measures of sleep apnea, hypopnea or glucose.

Conclusion: Hippocampal nighttime responsive neurostimulation therapies did not appear to worsen measures of normal or abnormal sleep.

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Keywords: Stimulation, Sleep, Central, Obstructive, Glucose, Insulin

1. Introduction

The responsive neurostimulation system (RNS, NeuroPace, Mountain View, CA) reduces self-reported seizure frequencies in patients with drug-resistant focal epilepsy [1]. The RNS surveys electrocorticography, which is trained to recognize physician-selected patterns associated with seizure onset, and then triggers electrical stimulation(s) or therapies designed to help mitigate or ideally terminate seizure. Delivered therapies or detection-stimulation counts (DSC) can be used to study treatment efficacies. For example, in the same patient we discuss here, we were previously able to illustrate effects of mirtazapine on increased RNS DSC over both an hourly and daily timeframe [2]. Contemporary RNS programming detects and delivers therapies generously. In the open-label portion of the RNS pivotal trial [1] there was an average of 1175 DSC per day [personal communication]. In this study we used a similar technique to examine DSC and whether or not they correspond to collected polysomnographic data either in sleep staging or measures of sleep disordered breathing.

Obstructive sleep apnea (OSA) and epilepsy have high comorbidity rates and sleep apnea may worsen seizure control [3,4]. Sleep disturbance and deprivation is known to reduce seizure threshold and therefore treatment for OSA can improve seizure control in patients with drug-resistant epilepsy. During convulsive seizures in particular there may be cessation of breathing, particularly during the tonic phase. Independent of seizure-related apnea, it is not well known whether undertreated epilepsy aggravates sleep apnea.

In the medical device literature the apnea hypopnea index (AHI), a key measure of sleep apnea, increased after beginning vagus nerve stimulation (VNS) therapy [4]. In addition, episodic apneas occurred more frequently during VNS. A similar understanding of RNS effects on sleep apnea has yet not been published. Of interest though is RNS data that shows DSC to have a strong circadian pattern, peaking during nocturnal hours regardless of region of onset [5]. In that same study, long nocturnal seizure episodes were increased depending on seizure onset locations. Specifically, temporal neocortical and frontal lobe onsets were more often at night while mesial temporal onsets were more often during daytime.

2. Materials and methods

With informed patient consent, patient data were abstracted and assessed from electronic medical records including RNS logs of DSC and polysomnography (PSG), average DSC, apnea events and other polysomnogram highlights, and stage of sleep were collected [Figs. 1 and 2]. Sleep was scored according to American Academy of Sleep Medicine (AASM) criteria by a licensed sleep medicine technician and further reviewed by a board certified physician specializing in sleep medicine. RNS stimulation settings at the time of polysomnogram included a current of 3.5 ma frequency of 100 Hz, a pulse width of 120 μs, and burst duration of 100 ms with an estimated charge density of 1.3 μC/cm². Therapies 1–5 were all the same, and the electrode...
configuration and polarity of right and left hippocampal contacts was negative with the RNS device positive. Detection settings on both hippocampi included bandpass assessments with bands set between 2–125 Hz, amplitudes of 12–69% and surveillance durations of 0.256–0.640 s. When first programmed at these settings, post stimulation therapy testing elicited no symptoms. Given the patient had a functional continuous glucose monitoring system with tissue glucose checks every 5 min (CGM, DEXCOM, San Diego, CA), that convenience data was also examined in relation to the RNS and polysomnographic findings. Statistical analysis was formed using two-tailed t-tests or Pearson correlation with significance \( p < 0.05 \).

3. Case report

A 45-year-old female with drug-resistant bitemporal epilepsy underwent implantation of the RNS device in 2014 after failure of medical and VNS therapies. Seizure types include audiogenic (Johnny Cash’s song Ring of Fire, for instance, would trigger focal seizures and potentially convulsions) as well as focal impaired awareness seizures characterized by automatisms of lip smacking and behavior arrest with rarer progression to bilateral tonic-clonic seizures. Her ILAE classification is focal aware and focal impaired awareness seizures with emotional, sensory and behavior arrest with progression to bilateral tonic-clonic seizures. A brother and a second cousin also have epilepsy, however the family LG1 gene status is unknown. MRI scan pre-RNS showed mesial temporal blurring and size diminishment on the left. Comorbid conditions include type I diabetes mellitus, depression, and insomnia. Her RNS detections were recorded from two four-contact depth electrodes placed over the left and the right hippocampus. Those locations were chosen based on intracranial monitoring results suggesting hippocampal involvement in seizure generation. Her VNS device, which historically produced no effect on seizure controls, remained off. A functional insulin pump was used for the duration studied as well as a regularly calibrated CGM.

Because of complaints of non-restorative sleep and excessive daytime sleepiness, she underwent polysomnographic testing in an AASM accredited lab. Sleep data was matched to RNS and CGM data during polysomnography. Anti-seizure medications included topiramate, levetiracetam, clonazepam, and gabapentin and were dosed at 09:00 and 21:00. The patient was not on antidepressants during this time period.

No clinical or electrographic seizures were observed by RNS or the 6-lead polysomnographic EEG. The RNS recorded many DSC throughout the night [Fig. 1]. These were not analyzed by side of detection. DSC failed to impact staging of sleep, with progression through various sleep stages independent of DSC activities.
DSC counts show a marked increase between 05:00 and 07:00, when hourly glucose averages were lowest at 80 and 74 mg/dL respectively. Blood glucose levels averaged 110 mg/dL (range = 68–172 mg/dL) during the sleep study. The lowest number of DSC was detected between midnight and 1 am, when 31 detections occurred (we only have hourly recordings of DSC, not minute-by-minute data). Blood glucose levels were recorded over that same hour averaged 114 mg/dL. DSC relationships show more stimulations with lower glucose (Glucose mean 111 mg/dL, SD 29, DSC mean 68, SD 39, Pearson R score = -0.685, \( p = 0.06 \)).

The PSG showed no significant sleep apnea [Fig. 1]. The AHI was 1.8 (an AHI of <5/h is considered normal). She slept for 6.6 h with a normal sleep efficiency of 90%, sleep latency was 21 min, REM sleep latency was prolonged (184.5 min). N1 sleep was 6.7% with 8.7 arousals for hour. REM sleep was reduced at 9% and stage N3 was increased at 38.6% of time. No significant heart rate or oxygen derangements were noted. During the entire night, a mixture of obstructive apneas (#5), central apneas (#6), and one hypopnea were recorded. All obstructive events occurred in stage II sleep over a 14-min period.

Most central apneas rapidly altered the sleep stage towards wakefulness.

Glucose values as close to the exact time of events were also recorded [Fig. 1]. Levels of glucose with obstructive apnea glucose levels \( n = 5 \), average = 115 mg/dL, range = 115, SD = 0) were higher than glucose levels with central apnea levels \( n = 6 \) average 97 mg/dL, range 71–109, SD13.8, \( t = 4.88, p < 0.01 \) two-tailed t-test).

4. Discussion

In this patient, there was no obvious link to RNS stimulations and detections from bi-hippocampal locations on measures of sleep apnea or sleep staging. Hourly DSC were highest when hourly glucose was lowest. We are now studying those relationships between RNS stimulations and glucose levels in separate work. Glucose levels, not DSC, appear to be more related to apnea. Specifically, central apneas are associated with lower glucose than obstructive apneas.

There are drawbacks to the study. First the patient does not have sleep apnea and whether or not the RNS worsens (or improves) insomnia, controls of sleep apnea, or sleep staging is unclear, there is no internal control (i.e. baseline polysomnogram without her RNS device) for comparison. Second, the time blocks available through RNS data access do not permit a minute-by-minute breakdown of DSC. The period between 1 and 2 AM for instance, when the bulk of the obstructive apneas and modest DSC occurred, cannot be further examined to see if DSC cluster peri-, inter-, or immediately post-apnea. Similarly we can't match the exact times of DSC to assess if central apneas are more likely with frequent stimulation. We can match glucose with apnea times, and there may be a difference there, though we view that relationship with some skepticism as all the obstructive events occurred in a 14-minute window with an invariant glucose level (Fig. 1). Further work in a broader population would need to clarify if central apneas consistently occur with a lower or declining glucose than obstructive apneas. A criticism of our statistical data would be risks of multiple comparison errors including comorbidities and the effects of medications on sleep. Effects of her complex medication regimen on sleep staging. Finally, sleep under laboratory conditions may have been atypical. In the Spencer et al. study, DSC counts by time of day suggest an increase during sleep, and decrease during wakefulness [5]. The patient’s own DSC data suggests that pattern is inverted, DSC are increased during daytime (see days 1–6 in Fig. 2). If that pattern held for our patient, the results may suggest that the patient had a sleep wake inversion, sleeping more during the day, and yet complaining of insomnia at night. She did not complain of daytime napping prior to the polysomnography, though subsequent use of daytime neurostimulants ( modaflan) caused her more recent DSC to show a more typical increase during night-time sleep and decrease during daytime (data not shown) with marked improvements in daytime somnolence.

Fig. 2. Detection stimulation counts recorded during the week of the sleep study. The polysomnogram was done from hour 2300 day 6 into hour 0700 day 7. The superimposed red markers are time of day, 0–2300 h.
We conclude that RNS effects on sleep seem to be minimal based upon the patient’s ECoG recorded from the hippocampal location. However, sleep staging like episodes of apnea may involve deep midline anatomical structures (pontine, medullary, thalamic, and hypothalamic) that are more remote from this patient’s hippocampal DSC or be remote from the patient’s individual epileptogenic network. This would align with earlier data on seizure Long Episodes recovered from hippocampal locations showing minimal diurnal variation as compared to other locations of electrode placement [5]. In comparison, it is important to note that brainstem and thalamic pathways are more involved with VNS stimulations [3,4] which may provide greater anatomic specificity for VNS effects on sleep apnea.

Conflict of interest
This paper has no financial support. Katie Kinnear as well as Drs. Doherty and Gersappe have no disclosures. Nicole Fortier has consulted for NeuroPace.

Ethical statement
Informed consent was obtained for this case write up and the work has been carried out in accordance with The Code of Ethics of the World Medical Association.

Acknowledgements
The authors would like to thank Chad Hamilton and Derek Schulte, NeuroPace, Mountain View California for aid in providing data.

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