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Case Report

Continuous monitoring devices and seizure patterns by glucose, time and lateralized seizure onset☆

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ABSTRACT

Objectives: To investigate if glucose levels influence seizure patterns.
Materials and methods: In a patient with RNS/NeuroPace implanted bi-temporally and type 1 diabetes mellitus, seizure event times and onset locations were matched to continuous tissue glucose.
Results: Left focal seizure (LFS, n = 22) glucoses averaged 169 mg/dL, while right focal seizure (RFS, n = 23) glucoses averaged 131 mg/dL (p = 0.03). LFS occurred at mean time 17:02 while RFS occurred at 04:23. LFS spread to the contralateral side (n = 19) more than RFS (n = 2).
Conclusion: Seizure onset laterality and spread vary with glucose and time of seizure.

1. Introduction

In people with epilepsy, the inter-relationship between glucose and seizure provocation is not well understood. Glucose is an important energy source during seizure, nonketotic elevations may predispose to focal seizures while failure of glucose transport into the central nervous system can predispose to epilepsy [1,2]. Regional glucose uptake or hypometabolic changes in possible epileptogenic tissue may become evident with 18F-fluoro-deoxyglucose (FDG) positron emission tomography (PET) mapping [3]. In patients with type 1 diabetes mellitus (T1DM), seizures may be provoked with hypo-, hyper- and ketotic glycemia [4–6]. Yet how alterations in glucose change seizure susceptibility is not well described.

The responsive neurostimulation system (RNS, NeuroPace, Mountain View, CA) reduces self-reported seizure frequencies in patients with drug-resistant focal epilepsy [7]. 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. Depending on where the electrodes are placed, the device can survey and record two different locations for seizure activity. That time-stamped data uploads to an online-accessible format for provider review, including if the stimulation failed and the event turned into an obvious electrical seizure.

In diabetes management, continuous glucose monitoring (CGM) is increasingly used to target insulin dosing and glucose response [8,9]. Dexcom monitoring systems (San Diego, CA) can continuously survey tissue glucose with data uploads every 5-min to an online repository [9]. CGM estimates tissue glucose and needs near daily calibration between the device and blood glucose (finger sticks) surveyed with a separate functional glucometer. Our index patient has both the RNS and CGM devices, she regularly calibrates her CGM and the two devices are time synchronized. We assume, based on humans and animal models, that tissue glucose parallels glucose availability to the central nervous system [10,11]. From studying these data sets, we aim to describe relationships between tissue glucose and seizures in this patient.

2. Material and methods

After informed consent medical histories including data from CGM and RNS devices were studied in a patient with drug-resistant bitemporal epilepsy and T1DM for relationships between left focal seizures (LFS) or right focal seizures (RFS) by outcomes time of seizure and glucose. Consecutive RNS long events (LE) were reviewed by a board certified Epileptologist and considered as seizure proxies. Seizures were not studied unless glucose data was available at the time of seizure, only one seizure per day, the first, was used. The closest CGM reading prior to seizure onset was studied (tissue glucose is typically recorded every 5 min). Ultradian trends in glucose were also studied immediately after seizure and in the hours prior and post-seizure. In this study, tissue glucose was considered a proxy for glucose levels within the central nervous system.

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A control group was set up based on random date generations during the study period at the exact time of left or right focal seizures. I.e. for every seizure detected off the left or right side, a control glucose from different date was assigned based on the exact event time provided that no seizure on the control day occurred and that glucose data was available. Two controls were studied, one based only on glucoses from seizure-free times matched to LFS or RFS seizure times, and a second based on glucose from seizure-free times matched to any seizure. Two-tailed independent sample T-tests were run with variables including tissue glucose by side of seizure onset and control. Trends in tissue glucose in the hour prior to and post-event were studied with Chi^2.

3. Results

A 47-year-old female with drug-resistant bitemporal epilepsy and T1DM underwent implantation of the RNS device after failure of medical and VNS therapies. Seizure types include audiogenic/reflex Johnny Cash's **Ring of Fire**, for instance, would trigger events of impaired awareness. Independent events characterized by automatisms of lip smacking and behavior arrest and possible progression to bilateral tonic clonic activities were also noted. The LG1 gene, GLUT1 and Anti-GAD antibody status remains unknown. Epilepsy onset was at 18 years, her diabetes at age 31.

Brain MRI scan pre-RNS showed left mesial temporal blurring and size diminishment and an absence of diabetes-related ischemic disease. Comorbid conditions include depression, hypothyroidism, inflammatory bowel disease and insomnia. An ineffective VNS device remained off.

Two prior scalp EEG studies showed a breakdown of diffuse onset and poorly localized (central/temporal or frontal) RFS ($n = 6$) and one likely left temporal event. The left hippocampus was an obvious site for RNS electrode placement based off of intracranial data, six seizures originated there. The second RNS electrode site proved more difficult. Only one intracranial subclinical event was recorded off of a right lateral inferior temporal location at an edge-of-grid location. Frequent interictal hippocampal discharges from the right hippocampus were noted. The second electrode was placed in the right hippocampus, assuming that place would prove important either as a generator or as a network hub for seizure spread.

An insulin pump and a regularly calibrated (average 2.4 times a day) continuous glucose monitor (CGM) were used during the study period. Anti-seizure medications used during this period included topiramate, levetiracetam, clobazam, clonazepam, and gabapentin. Dosing and timing of those medications varied little in the March 2016–October 2017 study period.

Insulin dosing varied by daily glucose reads. Day glucose targets were 70–180 mg/dL while night targets were 80–150 mg/dL (Fig. 1). No emergency presentation or lab findings to suggest nonketotic hyperosmolar hyperglycemia, ketotic hyperglycemia, or critical hypoglycemia occurred during the study period. The only hemoglobin A1C drawn during mid-study period was 7.3% (normal range 4–5.6%). Hourly glucose trends by 90-day blocks along with target glucose thresholds are depicted (Fig. 1).

RNS detectors off of both left and right hippocampi were changed once to enable more detections off of the left hippocampi. Stimulation settings were changed five times with four program changes to increase charge density and once to decrease stimulation frequency (settings not shown).

A total of 45 seizures were recorded from the lateralized hippocampal electrodes, 22 LFS and 23 RFS. Seizures showed no seasonal or monthly trends apparent in frequency or onset location. Seizures were least likely between 6 AM and 4 PM, a time in which glucose in general was normal or hyperglycemic (Fig. 2). The average glucose closest to time of seizure was 150 mg/dL, those levels were measured on average 2.3 min prior to seizure onset. The average glucose at the next CGM reading post-seizure was 149 mg/dL and occurred on average 3.27 min post-seizure. Glucose levels for LFS showed a mean of 169 mg/dL (SD = 66.3), for RFS 131 mg/dL (SD 41.5, $t = 2.29$ $p = 0.03$ 2-tailed T-test). With comparison to control groups, only the right side showed significance (Table 1). The mean time of seizure for LFS was 17:02 and for RFS was 4:23, though time plots suggest closer acrophasic clusterings of seizures than the mean levels, LFS in the evening, RFS from midnight until 4 AM (Fig. 2). These times are similar to her historic other ultradian patterns, specifically evening wake and early AM sleep and PM elevations in glucose and midnight until 7 AM declines in glucose (Fig. 1). Interestingly, LFS were of greater intensity, 19 of 22 events spread from left to right hippocampi, while most RFS remained unilateral, with only 2 of 23 spreading to the left side.

Not all seizures had obvious glucose trends in the hour prior to or post-seizure. If glucose levels were falling in the hour prior to seizure ($n = 14$), the event was more likely to be a RFS, if they were rising ($n = 15$) the event was more likely to be a LFS ($p = 0.02$, $Chi^2 = 5.85$). In the hour after seizure, no similar patterns were seen ($p = 0.28$, $Chi^2 = 1.16$). Regardless if LFS or RFS occurred, glucose tends to fall post-seizure ($n = 26$ down, $n = 6$ up). Hypoglycemia (defined as <70 mg/dL) associated seizures were uncommon, two occurred with glucose at 48 and 62 mg/dL; all were unilateral RFS. Twelve hyperglycemic (in this study >180 mg/dL) seizures were seen with a LFS:RFS of 9:3.

Somogyi effects of post-hypoglycemia rebound to hyperglycemia were not noted, for instance summer 2016 shows the most AM hypoglycemia, yet the post-hypoglycemia rebound varies little between 90 day epochs (Fig. 1). Three seizures occur summer of 2016, they clustered around midnight with an average glucose of 167 mg/dL.

4. Discussion

This is the first paper to our knowledge that looks closely at seizure and glucose at time of seizure events in an ambulatory patient. The data is most significant for right side events showing lower glucose (but not hypoglycemia) than control at time of seizure. This data remains unique, intriguing and impossible to collect without continuous surveillance devices. The clinical implications of tighter PM and pre-sleep glucose controls were suggested to hopefully avoid her larger left-sided seizures. The impact of those changes on her seizure patterns remains to be seen. Important questions are raised by this case study.

4.1. Are there nonketotic glucose levels – high or low – that predispose to seizure?

We reviewed the literature on glucose levels and seizure provocation in humans. Almost all of it documents post-event or intra-event glucose such as in status epilepticus, and almost none of it clarifies glucose at seizure onset or prior to events. In 53,505 emergency responses to seizure, when glucose was checked, only 1% of presentations had finger sticks of ≤60 mg/dL, while the average was 112 mg/dL suggesting that *most seizures occur with a relatively normal glucose* [12]. That study did not report hyperglycemic presentations. In neonates with hypoglycemic seizures, ≤50 mg/dL is considered low [13]. In children with complex or prolonged febrile seizures, 10% had stress hyperglycemia post-event, defined as ≥150 mg/dL [14]. Data correlating what levels of nonketotic hyperglycemia are associated with seizure provocation is harder to find, most series are small, post-event and range from 300 to 900 mg/dL [15,16]. Importantly, serum glucose and CSF glucose are likely different, serum runs higher than CSF, we would speculate a similar relationship to tissue (as measured by CGM) and CSF glucose [11]. What is absent from the literature are glucose levels that differ by *locations of onset in patients with epilepsy*. Perhaps the most relevant cite is in children with Landau–Kleffner syndrome (continuous spike and wave discharges during sleep) where ultradian *and* regionalized glucose utilization (either hypo- or hyper-metabolic changes) was seen with FDG-PET during wake and sleep [17].

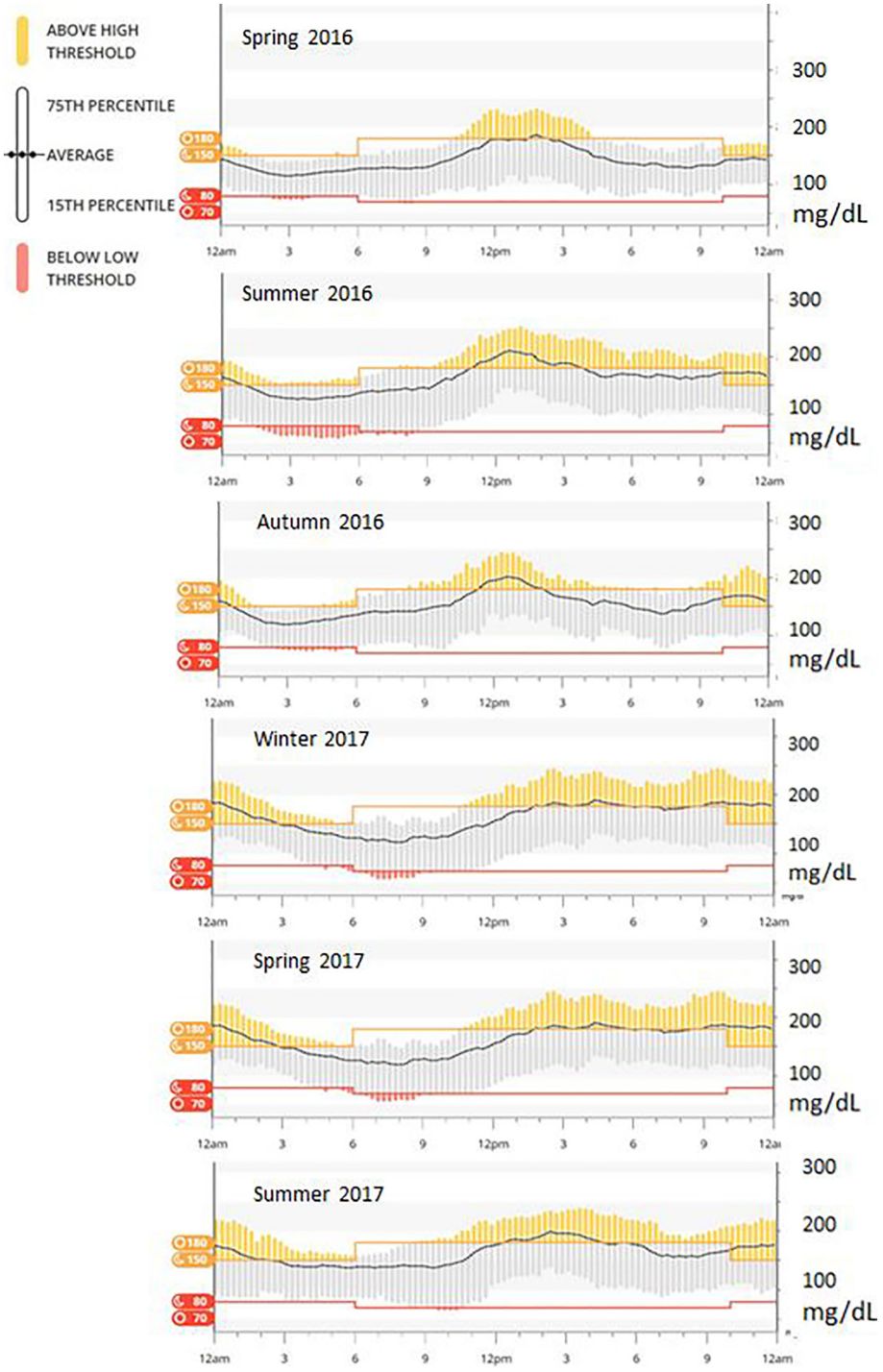

Fig. 1. Glucose trends by hour averaged into 90 day blocks during the study course. The yellow line is target maximum glucose level, <150 mg/dL during sleep and <180 mg/dL during the day. The orange line is target minimum glucose >80 mg/dL during sleep and >70 mg/dL during day. The black line is the average glucose by hour, the gray line spans 15th–75th percentile and any yellow vertical bar suggests an average above threshold, while red vertical bar suggests an average below threshold. PM showed consistently higher sugars than AM.

4.2. What's the relationship between type I diabetes mellitus and epilepsy?

T1DM is comorbid with epilepsy, with a hazard ratio of 2.89 [4–6]. Most T1DM patients are diagnosed with diabetes on average 2.8 years prior to their epilepsy, in this patient, the opposite was true [4]. Independent of risks of seizure from low or elevated glucose levels, individuals with T1DM may be prone to reflex epilepsy, our patient has a history reflex/audiogenic seizure, though we do not know which of her seizures were audiogenic to then correlate her glucose or laterality with [18]. There may be shared autoimmune risks due to anti-GAD antibody present in up to 80% type I diabetics and 6% of people with epilepsy [4–6]. GAD helps convert glutamate to gamma-aminobutyric acid (GABA), that process is contingent also on glucose through citric acid cycles. We do not know if this patient has anti-GAD antibodies.

4.3. Glucose manipulation as anti-seizure therapy, are there examples?

Anti-seizure diets such as low glycemic, modified Atkins or ketogenic all rely on marked reduction in carbohydrates and promotion of fat metabolism with the aim being ketosis and/or glucose lowering

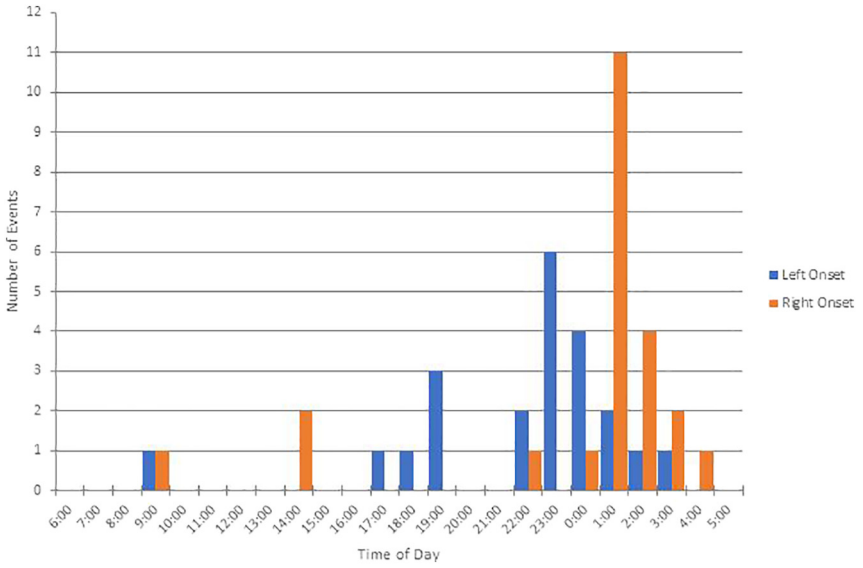

Fig. 2. Number of events by hour of day and side of onset.

[19]. Ketosis involves acetoacetate, acetone and β-hydroxybutyrate formation, which in turn helps lower pH and glucose utilization, which diminishes seizure activity. Anti-seizure drugs can alter glucose utilization. Oral glucose tolerance testing post-IV valproic acid (VPA) infusions show rapid decrement of serum glucose, perhaps suggesting alternate VPA mechanism(s) of action [20]. Similarly when lamotrigine was administered to patients with generalized epilepsy, regionalized decreases in FDG-PET uptake were noted [21]. Topiramate is associated with clinical weight loss, seizure betterment and improved glucose control [22]. Anti-diabetic medications may also alter seizure control, in animals, metformin, a medicine used in type 2 diabetes mellitus for chronic glucose lowering, shows promise in decreasing seizure severity and duration [23].

This study, however, shows a differential between side of seizure onset and glucose levels, with one side, the right, consistently lower in glucose at time of seizure than the left. In our patient this implies a more complex relationship than seizure betterment by glucose lowering.

4.4. Do ultradian influences help provoke seizure-induction?

Focal seizure susceptibility is influenced by circadian and ultradian cycles mediated through posterior hypothalamic networks, specifically with GABA releases which are thought to effect slow wave sleep, arousal states and their associated EEG changes [23,24]. Because of insomnia, in April of 2016, this patient underwent a one night polysomnography test. In that study, the longest duration of sleep stage was in slow wave/stage 3, from midnight until 4 AM, a time which overlaps with the majority of RFS, which remain the most intriguing for a glucose relationship/provocation. (Fig. 2) [25]. A one night study is unlikely to represent this patient's sleep during the study, but may at least permit speculation about how sleep staging could drive a sleep vs. wake glucose requirement in differing brain areas.

Perhaps the most relevant data on this shows localized but not lateralized ultradian patterns in a recent study of seizure times in RNS patients. Neocortical temporal and frontal onset patients showed seizure increases between 00:00 and 05:00 AM, and mesial temporal patients more often displayed seizure activity in day/wake time [26].

Our index patient has similar ultradian trends (Fig. 2). Our patient's left temporal times match what Spencer et al. describe for mesial temporal patients. If we assume our patient's second zone of seizure generation is neocortical *based on timing of events*, her right hippocampal recordings of seizure may document spread rather than seizure onset. As a reminder, her pre-RNS intracranial localization showed only one subclinical right-onset event from a neocortical temporal edge-of-grid

Table 1
Glucose levels at time of seizure as well as immediately after seizure by side of detected seizure.

	Average time of onset	Average glucose at time of seizure mg/dL (range, SD)	Average difference between time of prior tissue glucose and time of seizure, minutes (range)	Comparison of left to right onset glucose at time of seizure	Comparison of side of onset glucose to either control side glucose or all control glucose	Average glucose after seizure, mg/dL (range, SD)	Average difference between time of seizure and post-tissue glucose, minutes (range)	Comparison of left and right onset glucose levels immediately post-seizure
Any seizure N = 45	10:34	150 (48–272)	−2.3 (0 to −5)			149 (52–261)	3.27 (0 to 7)	
Left onset seizure N = 22	17:02	169 (82–272, 66.6)	−2.2 (0 to −5)	t = 2.31, p = 0.03		166 (82–261, 62.7)	3.5 (1 to 7)	t = 2.19, p = 0.04
Left control N = 22	17:02	159 (87–233, 42.5)			t = 0.58, p = 0.56			
All control	10:34	165 (84–253, 50.4)			t = 0.3, p = 0.79			
Right onset seizure N = 23	04:23	131 (48–205, 41.5)	−2.6 (−1 to-4)	t = 2.31, p = 0.03		131 (52–203, 41.2)	3.1 (0 to 5)	t = 2.19, p = 0.04
Right control N = 23	04:23	170 (84–253, 57.4)			t = −2.63, p = 0.01			
All control N = 45	10:34	165 (84–253, 50.4)			t = −2.94, p = 0.01			

location and her right-sided scalp localizations were poorly localized over anterior temporal locations.

4.5. Is there a network that links ultradian cycles, glucose levels and seizure onset locations?

If there was a linking network between cortex, wake/sleep regulation and glucose control one might presume the hypothalamus must be involved. The arcuate nucleus and lateral hypothalamus help regulate wake–sleep states and feeding behaviors [11,23,24,26–30]. Orexin, a key arousal/feeding/wake/sleep influencing neuropeptide is synthesized in the lateral hypothalamus and levels inversely correlate with serum and CSF glucose [11,30]. In rats, Orexin receptors are present in hippocampal CA-1 neurons and help trigger their firing [29]. Again from rat studies, orexin receptor mRNA is present diffusely in the brain — with locations varying from infra-limbic cortex, thalamus, and cerebral cortex suggesting diffuse pathways into epileptogenic tissues that might mediate ultradian and glucose influences [30].

4.6. What implications do these observations have for future work?

Given this data is convenient rather than common, cohorts of type-1 diabetics with both CGS and RNS are unlikely. Confirming this observation probably would require some step-wise approaches. Specifically, if there are lateralized *and* localized seizure onset times that differ from other RNS patients? If there are, what regions are most susceptible? And within those regions, from resected tissues banked from similar patients, might pathologies be demonstrated in pathways similar to what is seen in rat brain mRNA for Orexin similar neuropeptides or glucose receptors?

4.7. Hypothesis generated from this study include

A– Is there a kind of *glucostat*, where ultradian influences turn on right temporal neocortical vulnerabilities to seizure in the setting of a lowering glucose?

A correlate in a non-pathological state would be prioritizing glucose allocation for memory consolidation and storage during slow wave sleep. Meaning in much of our brains, network areas are turned off and on through an ultradian cycle — vision for instance is presumably not on/interpreted during sleep, nor is perhaps much of our sensory cortex, or even primary motor controls during REM sleep. However, areas that help with memory consolidation or dreaming *are* switched on during sleep and when they are, the glucose requirement presumably goes up. The pathology – in this case right neocortical seizure – becomes more likely when glucose is *lower* than usual, but only at a certain time during sleep. There is precedent for this, specifically in Landau–Kleffner patients that show lateralized glucose utilization varying by location and sleep/wake state [17].

B– Maybe the cyclic relationships are more important and the glucose observations are over-called?

The left hippocampus shows little variability with glucose compared to control, pre-sleep ultradian influences alone (Fig. 2) are perhaps more important for that location. The vast majority of times when this patient drops her glucose, seizures do not occur from the right side. Similarly, for most of the time when her glucose is elevated, her left hippocampus functions very well. Perhaps *infradian* effects compound seizure risks, most classically hormonal fluxes during menstrual cycling, and those effects might show a differential on neocortical vs. hippocampal tissues.

C– Maybe the glucose remains a peripheral tissue epiphenomenon, coincident and unrelated to seizure provocation by site or time of seizure?

4.8. Implications for surveillance devices

RNS therapies delivered *did not cause* clinically significant tissue glucose alterations. If there is a relationship between epileptogenic zone, glucose levels and ultradian cycles, the ability to read CNS glucose and seizure onset times may permit a finer tailoring of therapies and/or mapping of lateralized differences by ictal onset locations. Observations of seizure risk perhaps increasing in the hour prior to seizure based on glucose trends may be important, specifically in altering surveillance thresholds or for warning of heightened seizure susceptibility. Finally, elevated glucose and left hippocampal events more often spread contralaterally, implying that stimulation pathways for LFS in this patient should be stronger.

4.9. Concessions and limitations

There are numerous issues beyond our control in this study. For instance variable insulin dosing, time of anti-seizure drug use, setting changes on the RNS or CGM calibrations, the tendency of the RNS to overwrite long events or seizures, inability to otherwise correlate inflammatory, autoimmune, menstrual, circadian or ultradian variabilities, use of other medications, the inability to accurately measure glucose directly in our patient's CNS tissues (or alternatively delays between CGM tissue glucose vs CNS glucose) fat/protein/glucose/AED absorption issues in the setting of inflammatory bowel disease, and perhaps most importantly over the study duration, changes in her underlying epilepsy. We are assuming those effects randomize over the duration and number of events studied and with two-tailed statistical methods.

5. Conclusion

In this convenience sample a type I diabetic with hippocampal RNS electrodes showed variations by side of seizure onset that were both ultradian and related to tissue glucose. The right side, which we presume may be measuring neocortical seizures, shows perhaps the most vulnerability to glucose, with seizure provocation at relatively lower glucose levels and earlier AM times when compared to the control or left-sided data. Seizures (or RNS stimulations) do little to alter tissue glucose post-events. Further study of how glucose impacts seizure control will be important to further clarify this finding.

Conflict of interest

This paper has no financial support. Katie Kinnear as well as Drs. Doherty and Haltiner 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.

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