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CASE REPORT

Responsive Neurostimulation Effects Significant Seizure Reduction Without Resection in Medically Refractory Epilepsy Involving Occipital Networks. A Retrospective Review of a Case Series

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ABSTRACT:

Objective: The goal of this work is to retrospectively and qualitatively describe a case series of two (2) patients with Occipital Epilepsy Networks treated with Responsive Neurostimulation

Method: A retrospective qualitative review of two (2) clinical cases is presented and clinicopathologic features and quantitative Responsive Neurostimulation datasets and associated variables are analyzed for review

Results: Significant and incremental seizure reduction occurred post RNS placement and this report highlights these 2 cases. One patient exhibited no seizures subsequently 2.5 years post Responsive Neurostimulation placement (Engel class I) and another patient became almost free of seizures except for the occurance of fleeting and occasional visual auras approximately 2 years post Responsive Neurostimulation placement (Engel class II). This report highlights that these 2 cases exhibited good clinical outcome after Responsive Neurostimulation placement for epilepsy localized to onset zones in occipital networks.

Introduction: This article highlights case summary findings of 2 patients with the relevant datasets including histograms and metrics identified on RNS, neuroimaging, and EEG datasets after which a discussion and conclusions regarding these observations will be presented and discussed.

Case Summaries

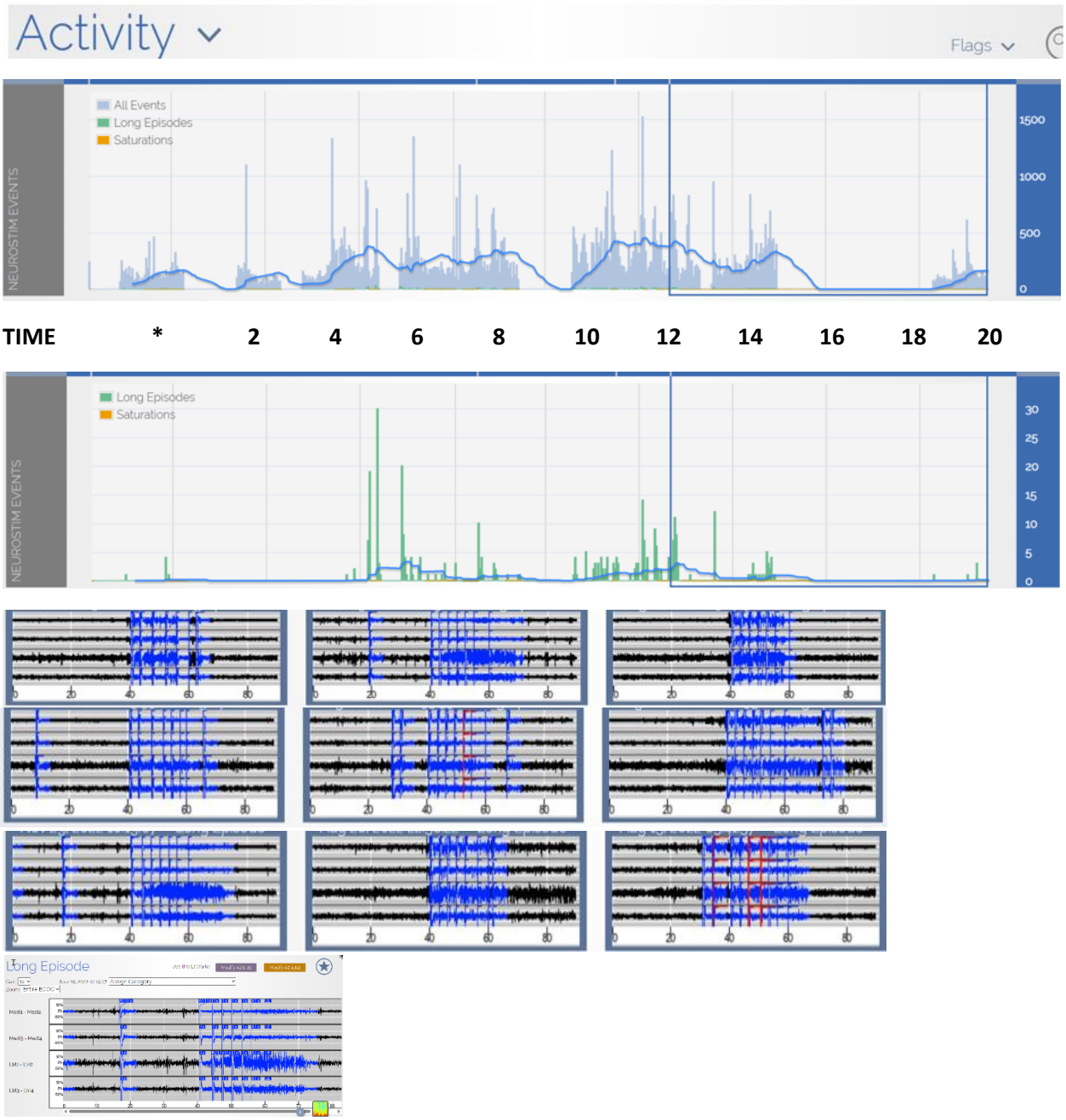
CASE 1: This patient presented to our service at age 47 years of age who already had well established lifelong intractable and disabling epilepsy. The patient was the product of a 72-hour or longer labor that did not progress normally and was believed to have a course consistent with resultantly sustained watershed strokes in the PCA/MCA distribution as noted below in the figures and exhibited lifelong cognitive impairment, psychomotor delay, and a clinical diagnosis of cerebral palsy. The patient's seizures begin with flashing lights, and then loss of awareness, blinking, and if prolonged may involve progression to Generalized Tonic Clonic Seizures (GTCS). Seizures occurred several times weekly despite medications with many generalized seizures yearly and due to these secondarily generalized seizures and falls and these required him to be wheelchair bound and he tried and failed numerous seizure medications. After surface EEG monitoring identifying posterior predominant network involvement and invasive EEG identifying those seizures emanated from the right occipital region with subsequent spread beyond that region, RNS was placed at age 49 in late 2019 as noted over the right occipital cortex as shown, see figures. After most the most recent programming approximately 22 months ago- no clinical or electrographic seizures have been noted on electrocorticogram review which previously identified long episodes and or Saturations of channels with last Long Episode noted approximately 10 months ago. At the time of this manuscript, he has not returned for followup as he has not had any significant clinical seizures, although family maintains that the patient experienced only a couple of minor sensory seizures with only visual auras but as such has not progressed to loss of awareness and or falls or GTCS, so this patient has acquired at least an Engel class II outcome at this time. Of note, the patient and family did not wish for investigation of a frontal lesion on the left anterior quadrant as they feared complications of intervention on the frontal lobe.

CASE 2: This is a patient who presented to us at approximately 35 years of age who experienced who exhibited intractable seizures that start with visual phenomena and seizures with progression to loss of contact and then the seizures would often secondarily generalize, and he and failed multiple seizure medications. He was the product of a forceps delivery in Africa who although had a fractured clavicle and a several day Neonatal Intensive Care Unit Stay, had a normal neurodevelopment until teenage years when he fell and sustained a traumatic optic injury losing sight in his left eye at age 15. He was noted to have seizures start in late childhood and seizures occurred approximately 2-3 seizures monthly with many secondarily generalizing yearly. He proceeded to RNS implantation at age 37 in late 2019 after having extensive evaluation showing occipital lobe onset seizures with spread to the posterior ipsilateral left temporal lobe many of which seizures secondarily generalized during the diagnostic sessions. The seizure onset zone was localized to the lateral region of the superior occipital lobe and RNS was positioned as shown – see figures. After most recent programming approximately 16 months ago- no clinical seizures were noted, no seizures were noted on electrocorticography and there were no Saturations of channels or Long Episodes noted

FIGURES-RNS ACTIVITIES

FIGURE A: HISTOGRAMS SHOWING ACTIVITY RECORDED BY RESPONSIVE NEUROSTIMULATION (NEUROPACE TM) FOR CASE 1

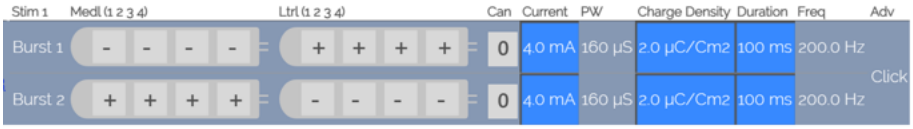
ACTIVITY- Note time is in months, * represents activation of RNS therapy



LEGEND: Top panel- showing total day to day histogram of all activities identified on RNS. MIDDLE: Long episodes and or saturations, day to day, BOTTOM: Most recent panels showing electrocorticograms of most recent long episodes or saturations (5 occurring in month 14 of RNS therapy, and the remaining episodes occurring in months 16-21)

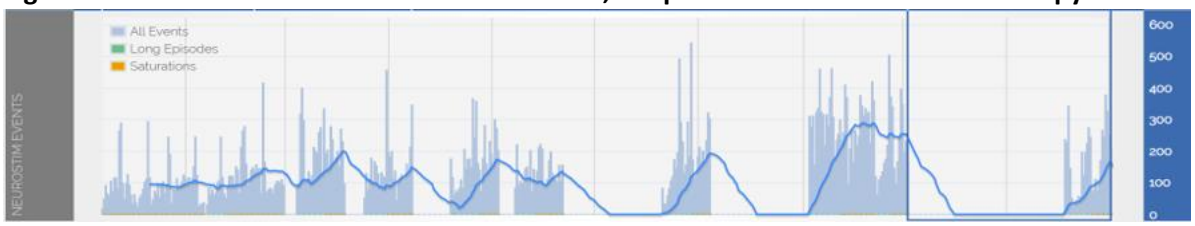
Case 1 Figure B: Documentation of Programming

2 most recent programming and detection configurations months 16-present and previously at month 15)

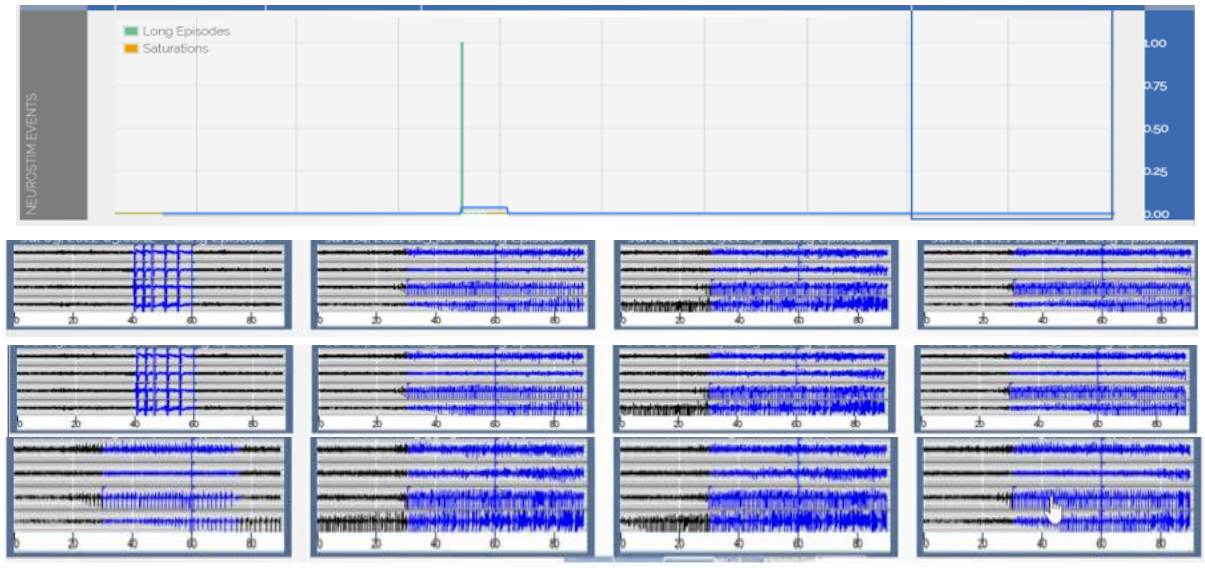


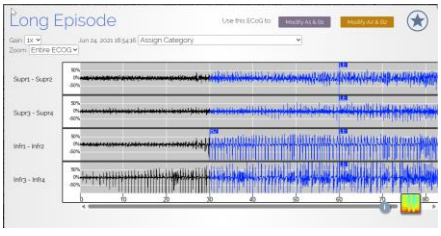
Electrodes (Lead1)(Lead2)(Can)	Current	Frequency	PW per Phase	Burst Duration	Charge Density	Detection Summary	Magnets per Month/ Total	Saturations per Month/ Total	Long Episodes per Month/ Total	Episodes per Day	Therapies per Day
Tx1:(----)(++++)(0)	Tx1:4.0 mA	Tx1:200.0 Hz	Tx1:160 µs	Tx1:100 ms	Tx1:2.0 µC/cm²						
(++++)(----)(0)	4.0 mA	200.0 Hz	160 µs	100 ms	2.0 µC/cm²						
Tx2:(----)(++++)(0)	Tx2:4.0 mA	Tx2:200.0 Hz	Tx2:160 µs	Tx2:100 ms	Tx2:2.0 µC/cm²						
(++++)(----)(0)	4.0 mA	200.0 Hz	160 µs	100 ms	2.0 µC/cm²						
Tx3:(----)(++++)(0)	Tx3:4.0 mA	Tx3:200.0 Hz	Tx3:160 µs	Tx3:100 ms	Tx3:2.0 µC/cm²	[A] Ch.1 LL(75%, 2s, 2m)	0/	0/	↓10.2/	↓248	↓248
(++++)(----)(0)	4.0 mA	200.0 Hz	160 µs	100 ms	2.0 µC/cm²	[B] Ch.3 LL(75%, 2s, 2m)	0	0 (Low)	75 (>20s)		
Tx4:(----)(++++)(0)	Tx4:4.0 mA	Tx4:200.0 Hz	Tx4:160 µs	Tx4:100 ms	Tx4:2.0 µC/cm²						
(++++)(----)(0)	4.0 mA	200.0 Hz	160 µs	100 ms	2.0 µC/cm²						
Tx5:(----)(++++)(0)	Tx5:4.0 mA	Tx5:200.0 Hz	Tx5:160 µs	Tx5:100 ms	Tx5:2.0 µC/cm²						
(++++)(----)(0)	4.0 mA	200.0 Hz	160 µs	100 ms	2.0 µC/cm²						

Figure A Case 2: ACTIVITY- Note time is in months, * represents activation of RNS therapy



TIME * 2 4 6 8 10 12 14 16 18

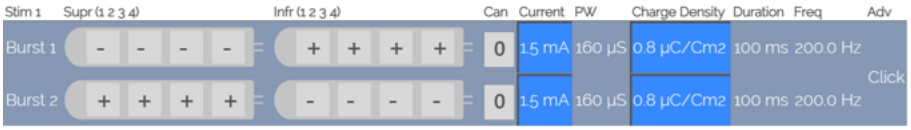




LEGEND: Top panel- showing total day to day histogram of all activities identified on RNS. MIDDLE: Long episodes and or saturations (most recently occurring in month 5 of therapy), day to day,

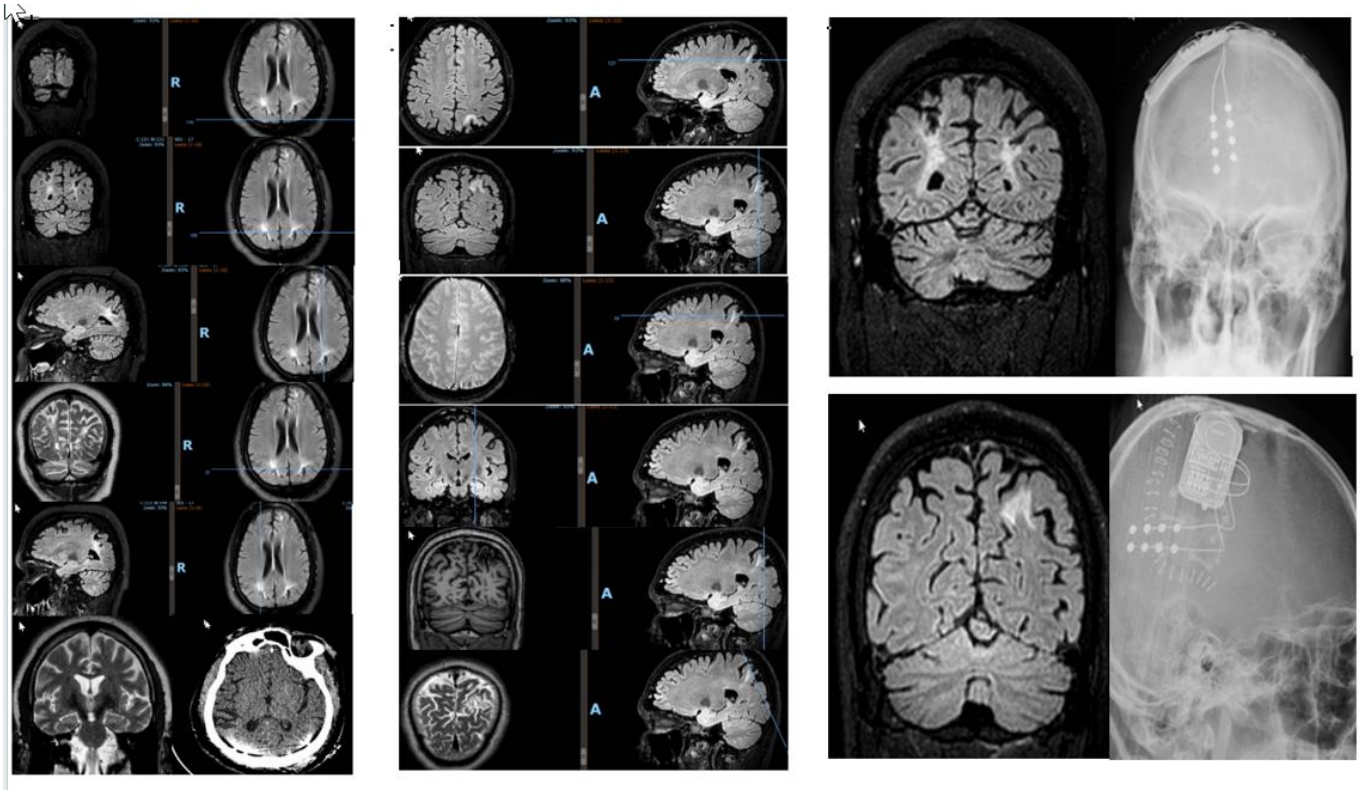
BOTTOM: Most recent panels showing electrocorticograms of most recent long episodes and or desaturations along with closer detail of a typical long episode correlating with a clinical seizure.

Case 2-The 2 Most Recent Programming and detection changes (top therapy starting in month 14-present, bottom therapy started approximately during month 4)



Electrodes (Lead1)(Lead2)(Can)	Current	Frequency	PW per Phase	Burst Duration	Charge Density	Detection Summary	Magne per Mo Total	Total	Episodes per Month/ Total	Episodes per Day
Tx1:(----)(++++)(0)	Tx1:1.5 mA	Tx1:200.0 Hz	Tx1:160 µs	Tx1:100 ms	Tx1:0.8 µC/cm²					
(++++)(----)(0)	1.5 mA	200.0 Hz	160 µs	100 ms	0.8 µC/cm²					
Tx2:(----)(++++)(0)	Tx2:1.5 mA	Tx2:200.0 Hz	Tx2:160 µs	Tx2:100 ms	Tx2:0.8 µC/cm²					
(++++)(----)(0)	1.5 mA	200.0 Hz	160 µs	100 ms	0.8 µC/cm²					
Tx3:(----)(++++)(0)	Tx3:1.5 mA	Tx3:200.0 Hz	Tx3:160 µs	Tx3:100 ms	Tx3:0.8 µC/cm²	[A] Ch.3 LL(88%, 1s, 2m)	0/	0/	0/	167
(++++)(----)(0)	1.5 mA	200.0 Hz	160 µs	100 ms	0.8 µC/cm²	[B] Ch.4 LL(113%, 1s, 2m)	0	0 (Low)	0 (>20s)	
Tx4:(----)(++++)(0)	Tx4:1.5 mA	Tx4:200.0 Hz	Tx4:160 µs	Tx4:100 ms	Tx4:0.8 µC/cm²					
(++++)(----)(0)	1.5 mA	200.0 Hz	160 µs	100 ms	0.8 µC/cm²					
Tx5:(----)(++++)(0)	Tx5:1.5 mA	Tx5:200.0 Hz	Tx5:160 µs	Tx5:100 ms	Tx5:0.8 µC/cm²					
(++++)(----)(0)	1.5 mA	200.0 Hz	160 µs	100 ms	0.8 µC/cm²					

FIGURE B: SELECTED NEUROIMAGING



LEFT PANELS: Case 1 Neuroimaging Figures- Coronal MRI Flair sections corresponding to Axial T1 MRI sections are noted (top 2 panels) followed by Sagittal flair comparison sections, along with coronal T2 MRI comparisons with bilateral sections thru the corresponding left and right axial Flair MRI bi-posterior MCA/PCA watershed region lesions or signal changes and the bottom panels show a coronal T1 section through the hippocampi showing relatively preserved mesial structures along with invasive electrodes on CT noted in situ at time of invasive EEG recordings. Of note there is a frontal signal on the left of unclear significance which was not investigated as noted.

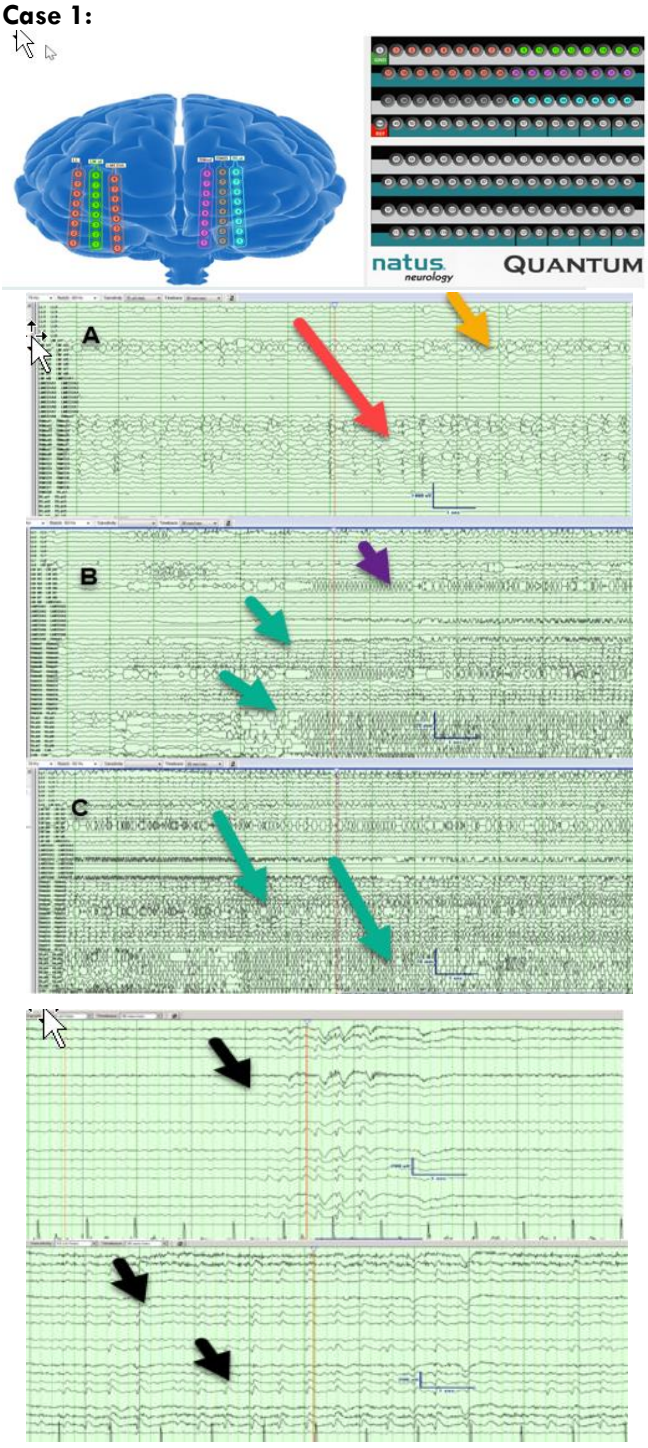
MIDDLE PANELS: Case 2 Neuroimaging - Comparison of sections of Axial Flair MRI, Coronal Flair MRI, Gradient Echo MRI sequences with

sagittal Flair MRI sequences along with a coronal section of mesial temporal lobe structures showing relatively preserved mesial structures, and sections of T1 coronal and T2 coronal sections thru the left posterior quadrant occipital lesion

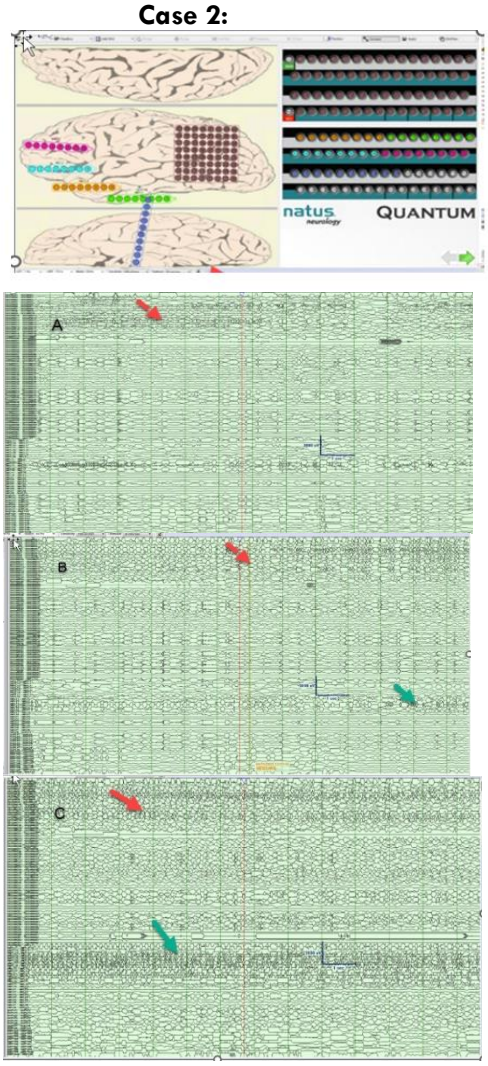
RIGHT PANELS: FIGURES showing CORONAL FLAIR MRI and AP XR Top Panel for Case 1 denoting vertically oriented superior/inferior RNS placement of the 2 -4 X1 strip leads in the right and midline occipital regions and CORONAL FLAIR MRI and LATERAL XR Bottom Panel for Case 2 denoting horizontally oriented RNS strips. Note that Both of the cases had occipital lobe onset seizures in the vicinities of the RNS placement and RNS lead placements correlated with zones of maximal amplitudes and or frequency of ictal onset discharges which were signatures of electroclinical seizures in these regions.

FIGURE C: EEG DATASETS

Case 1:



Case 2:



EEG FIGURE LEGEND.
LEFT PANELS: Case 1 Invasive EEG SERIES(A-C panels) showing relative electrode placement using XLTEK Quantum headbox and configuration. Note interictal Left sided occipital spikes and irregularities (Yellow arrow) and Right sided interictal spikes with irregularities (Red Arrow) and subsequent transient activity in the left ward mesial areas during a seizure with substantial volleys of seizure discharges that progress as noted (Green Arrows) Bottom 2 panels identify Surface EEG panels showing diffuse but posterior quadrant maximally interictal discharges (F) black arrows and ictal continuum correlating with similar activity distribution during seizure onsets identified on surface EEG monitoring.
RIGHT PANELS: Case 2 Invasive EEG SERIES(panels A-C) showing relative electrode placement using XLTEK Quantum headbox and configuration. RED arrows show seizure onsets in the vicinity of the noted left lateral occipital lesion regionally along grid contacts (see MRI/Neuroimaging figures) that subsequently propagate to temporal contacts (Green Arrows) identified during a typical seizure

Discussion: Literature identifies that RNS was FDA approved based on pivotal studies by 2014 in the US for partial onset epilepsy in patients with no more than 2 foci identified on invasive EEG long term monitoring in patients who had intractable epilepsy and were disabled due to the seizures, and post approval articles have highlighted that RNS is effective and demonstrated safety over at least a 9 year period although specifically no published extensively studied series of occipital network cases are published currently in the literature other than an abstract which was presented at the American Epilepsy Society in December 2022 as cited and discussed below. [1,2,3,4,5]

Occipital lobe seizures have been described in various clinical scenarios.[6-13] Occipital seizures may occur within symptomatic epilepsies such as cerebral palsy which may have diffuse pathology or be due to focal pathology such as lesions of various sorts including tumors, trauma, or inflammation and other pathologies(heterotopias, cortical dysplasias, polymicrogyria for examples) in the occipital region or may be occur as part of an idiopathic childhood syndrome such as benign occipital seizures, or with a suspected yet to be determined genetic etiologies such as in the Panayiotopoulos syndrome, as part of later onset childhood epilepsy with occipital paroxysms, or late onset childhood occipital epilepsy of Gastaut, or be associated with Lafora disease or mitochondrial disorders.[6-13] Occipital lobe epilepsy is relatively rare among patients with seizures as occipital onset seizures account for up to 10% of all epileptic seizures equally affecting all genders according to the current literature.[6,8,10,11] There is an association with celiac disease and gluten sensitivity noted in the literature. [6-10,11] Occipital lobe seizures may occur as in these noted cases as intractable epilepsy where patients take multiple anti-seizure medications yet continue to have episodic seizures and in particular the risk of hospitalization and need for multiple anti-seizure medications are features that the literature highlight in cerebral palsy. [15-17] There may be a noted subset of patients whose clinical course with non convulsive occipital onset seizures in the ICU population that may be associated with various genetic factors such as POLG and or neuroimaging changes, and photic stimulation induced seizures that may be otherwise associated with good and benign prognosis as long as such stimuli are avoided have also been described. [18-20]

Clinical features are due to the specific cortical localization of the seizures and may involve blinking, visual symptoms including visual field deficits, illusions such as Palinopsia or image repetition and involve Eye pain, Nystagmus, involuntary eye movement, and other features such as Nausea, and headaches that are particularly associated with the pre or postictal phases and there is a postulated potential interrelationship of migraine with the spreading cortical depression of Liao along with genetic factors impacting vasomotor tone and associations with cellular effects and occipital lobe epilepsy. [6-14,20-22]

Occipital seizures that result from the primary visual cortex result in what are termed focal sensory seizures that include bilateral loss of vision or positive or negative visual phenomena such as seeing colors or scintillations although bilateral loss of vision may occur in the form of a “black-out” or “white-out.” [6-14,19-22] Seizures localized to the extrastriate cortex, are associated with complex visual hallucinations that include vividly and often detailed pictures of objects and scenes, and these are termed “cognitive seizures.” [6-14,19-22] Epileptic nystagmus is associated with seizures at the parietal-occipital sulcus. Eye movements such as eye fluttering are common along with retained awareness, the head or trunk may also be involved but should seizures occur inferiorly to the calcarine sulcus, complex partial seizures or focal unaware seizures may occur and may involve spread to the ipsilateral temporal lobe. [6-14,19-22] Seizures that originate or involve regions superiorly to the calcarine sulcus may result in rapid synchrony or propagation and result in atonic seizures or other motor manifestations if there is propagation to the parietal or frontal lobes, and therefore such focal onset occipital seizures may become a secondarily generalized tonic clonic seizure and or evolve potentially to status epilepticus. [6-14,19-22]

The literature does not speculate what factors or how long focal posterior or occipital lesions might allow for connectivity to posterior temporal or temporal networks as case #2 potentially implicates such a mechanism here in this report. Case #1 EEG dataset highlights that although there are focal lesions in the posterior regions/occipital MCA/PCA watershed border zone territories, that there is a wider synchrony in particularly noted on the surface EEG suggesting a more extended epileptic network from the surface EEG recordings. Nonetheless, these cases highlight that responsive neurostimulation at the focally identified cortical areas of ictal onset was highly effective at mitigating clinical seizures for these patients.

Of note, the literature does not yet have an authoritative recommendation or “best practices” recommendation when or how to implement RNS definitively in occipital network disease although

when seizure medications are not effective or when resections that would impact vision would not be desirable- RNS remains an option as highlighted in these cases of this report.

These cases in this report represent 2 cases out of 25 cases with RNS Neuropace either placed at our institution or referred for such (8%) of which RNS was implemented overall initially at our institution starting at 2016. The goal at our institution was to offer RNS as an available FDA approved palliative treatment for intractable focal onset seizures proven by invasive EEG monitoring who were disabled, having tried and failed a number of medications with ongoing seizures which was commensurate with FDA approval and other accepted authoritative indications for use of the technology [1-4]. Although the literature notes an abstract published in 2022 at the American Epilepsy Society which denotes in 4 cases with occipital onset seizures an approximately up to 90 % seizure reduction, clinically noted Engel outcome as in our series being reduced to Class I or Class II- with either seizure freedom or no significant seizures after an approximately 2.5 year period post RNS treatment has not been previously reported. [5,23,24]

Similarly as in the cited abstract and articles regarding long term RNS treatment, it is noted that side effects were low with RNS in our cohort, and we report no infections or other surgical complications in this group, and similar transient visual auras or sensations occurred in these cases primarily during RNS programming that abated with either stopping or lessening stimulation either by attenuating the current or current density and other parameters although the specific datasets regarding such is not shown here. [1-3,5]

Note that this article postulates and assumes that the activities quantified on the daily histograms of the electrocorticograms of the RNS recordings represent surrogate markers of seizure activity either clinically and or electrographically as other articles also similarly assume. [25-27] The histograms notably contain multiple interictal discharges daily of unclear clinical significance(up to maximally 1500 such discharges daily) and such fluctuated over time and we acknowledge that at times the dataset may also be somewhat limited as these patients we speculate when they were doing well might not have upload data from the RNS devices regularly and or consistently for various time intervals- but nonetheless we quantified and displayed the daily inventories of ictal and interictal discharges that were available at the time of publication as well as the inventory containing short and long episode counts with channel saturations, and thus the daily histogram data counts as other articles do similarly- but we acknowledge that further research will be needed to determine the absolute clinical and biologic significance of such activities over time. [25-27]

Presently there are approximately 30 anti-seizure medications (ASMs) available worldwide.[28,29] Although such medications are available, for many patients these may pose intolerable side effects especially for patients with intractable epilepsy for whom multiple ASMs may be co prescribed since seizure freedom does not occur for some patients who are prescribed the ASMs.[28-30] The patients in this series had tried numerous and co-prescribed ASMS with side effects and incomplete seizure control and such clinical scenarios induce patients and providers to consider surgical treatment options when possible and to pursue other therapies for treating intractable epilepsy including Vagal Nerve Stimulation- which may be associated with a reduced medication burden in some patients but allows complete control of seizures in only up to 15 % of cases, and RNS, and other therapies[1-3,31,32]. Reports such as this series indicate that RNS, which is approved as a palliative therapy, is a method of treatment that may allow for improved seizure control although the mechanism of action ultimately that occurs on the cellular level and or what exact biological substrates are effected or targeted by the RNS device and or treatment remain unknown at this time.[1-3] Of note RNS is used specifically in bitemporal epilepsy where resection could result in an amnestic syndrome, and in focal epilepsies that involve the motor strip or eloquent and other areas since resections would produce paralysis or aphasia respectively or other neurologic or neurocognitive deficits, and in other widespread poorly localized epilepsies where resection would not be practical due to similar issues, or in seizures emanating from the visual cortices as this unique series highlights[1-4]. This series highlights that patients who were appropriately unwilling to undergo focal resections leading to visual field defects ultimately had an excellent outcome without such risks of resective surgery and negative impact or damage to visual fields ultimately which would be produced by focal resections.

The exact parameters RNS requires for treatment including current required, current density required, pulse width, frequencies and other parameters are not definitively known and there are no standards of care in these regards at this time definitively, but we wish to note that for the occipital cases we are reporting- electroclinical seizure reduction occurred with only modest neurostimulation (with 0.8 uC and 2 uC charge densities) although the exact reasons

are not known although we speculate that different cortical regions and or networks may have variable thresholds with respect to therapy but as such there is no systematic study or review or other such commentary or opinions available at this time. Another nuance raised by this case series is that it seems that focal seizures in the occipital region may have the potential to involve distal sites of propagation as highlighted in the first case which identifies a fairly widespread distribution of activity but particularly the 2nd case is highlighted where seizures propagate to the ipsilateral temporal lobe and whether or not such propagation from the occipital area will incite distal areas to the onset which may result in a kindling type of mechanism or chronic seizures begetting seizures and propagating pathology through such pathways via unknown mechanisms remains unknown, although speculation of such exists in the literature that such a phenomenon occurs[33,34]. Of note, the histograms of the day to day seizure activities for these patients may have some waxing and waning periodicity of seizure activity noted where there are days or weeks when counts are higher or lower and may occur in cycles potentially as other articles have noted but the underlying substrates and ramifications remain unknown.[1-4] This series also highlights that RNS devices may provide long term observational and monitoring data from the electrocorticogram that may allow for further study in the future as therapy longitudinally occurs over time as a means of having a system to monitor either the treatment and or development of such activation of distal networks or sites of involvement for potentially studying what is known as "kindling" highlighted above. [1-4,33-37] We speculate that there may be cases that could yield useful observations with both occipital RNS implantation and potentially ipsilateral temporal RNS implantation or other distal site implantation and that RNS implemented as localized not only cortically but placement as chronic stereo EEG and potentially DBS-deep brain stimulation in other regions such as in the thalami that could monitor and or modulate more diffuse neurologic networks.[1-4,33-37] Therefore there may be other cases in the future identified where RNS provides useful observation and treatment over time when placed either cortically or as in stereo EEG into deep structures but such speculations including what pathology would be ideal or what exact molecular substrates would be involved and the specific clinical ramifications and scenarios at present remain unknown at this time although literature regarding the overall research and clinical use of RNS technology in various circumstances and pathologies is evolving.[1-4,33-37]

Conclusion: This article highlights that RNS offered as treatment for focal onset occipital network epilepsy proven by invasive EEG monitoring in medically intractable epilepsy may be associated with an Engel Class I or II outcome after an approximately 2.5 year period in a retrospective review of a case series of selected patients.

Disclosures:

Note that a version of this work was presented as:
ABSTRACT 1383 IEC 2023, DUBLIN IRELAND
35th International Epilepsy Congress, Sept 2-6, 2023

Conflict of interest: no conflicts of interest relevant for disclosure

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