

Letter to the Editor

Unexpected increase of seizures in a patient treated with responsive neurostimulation: Check the lead!



The NeuroPace RNS[®] System provides closed-loop brain stimulation in patients with refractory multifocal epilepsy who are not candidates for resective surgery. The system acts as a sensing and stimulation device by continually monitoring the intracranial EEG (ICEEG) at the seizure focus and delivering brief electrical stimulation pulses as soon as an epileptiform activity is detected. Typically, two depth and/or subdural cortical strips are implanted in the epileptogenic focus. We report here a patient who presented with an acute increase of seizure frequency as a consequence of a lead break, which was not visible on CT scan. Retrospectively, the lead break was confirmed by an increase in lead impedance and presence of artifacts on the ICEEG recordings.

A 39-year-old right-handed male was referred to our epilepsy center for medically refractory epilepsy. His seizures were characterized by an aura, which was described as rising or squeezing sensation in his stomach followed by impairment of consciousness, occasionally evolving into a generalized tonic-clonic seizure. His seizure frequency was 3–7/week despite receiving adequate trials of several antiepileptic medications. Fluid attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) revealed bilateral increased signal within the mesial temporal structures, suggestive for bilateral mesial temporal sclerosis. Fluorodeoxy glucose positron emission tomography (FDG-PET) imaging showed mild to moderate hypometabolism in the bilateral temporal lobes. Video-EEG captured left and right seizures with frontotemporal onset. After discussion at a multidisciplinary patient management conference, it was concluded the patient had bitemporal epilepsy and was offered treatment with responsive neurostimulation. In July 2008, the patient was enrolled in a prospective, multi-center, double-blinded, randomized, sham-stimulation-controlled pivotal study (Heck et al., 2014). In July 2008, the RNS leads were implanted bilaterally in the mesial temporal structures. Patient responded to the treatment and experienced a 50% decrease in seizure frequency (from 5/week to 2/week). In April 2009, the patient reported a sudden unexplained increase in seizure frequency and the seizure diary indicated a mean seizure frequency of 9/week. There were no acute triggers identified, such as a febrile episode or non-compliance to his anti-epileptic drug treatment. At this point, a technical problem with the neurostimulator was suspected. CT scan of the brain was performed and showed correctly placed leads in the mesial temporal structures. Standard radiography could not show any abnormality of the stimulations leads. Despite the negative investigations, a surgical revision of the device was performed. The neurosurgeon found a fracture of the right lead at the level where it was tethered by the burr hole cover.

Two weeks following lead replacement, seizure frequency returned to post-stimulation seizure frequency.

Retrospectively, the impedance values of each contact of the left and right hippocampal electrodes were reviewed. The mean impedance of the four left contacts remained stable throughout the follow-up, with an average value of 468.68 Ohm (range 435.75–509.25 Ohm, SD $\pm$ 15.01). On the right side, a sudden unexplained increase of impedance was measured in March and April 2009. In fact, in 2 of the 4 contacts no impedance could be measured, indicating a discontinuity in the stimulation loop. Before the suspected lead break, mean impedance value was 718 Ohm (range 596–946 Ohm, SD $\pm$ 53.19). In March (3/20/2009) and April 2009 (4/9/2009), impedance reached high values to 3008.25 Ohm $\pm$ 350.25. The patient reported an increase in seizure frequency from 4th April 2009 onwards, demonstrating a time lag of 15 days between lead impedance increase and loss of therapeutic effect.

The artifact corresponding to the lead break was also identified on the ICEEG recordings recorded by the RNS device. Fig. 1a shows normal interictal left (upper two) and right (lower two) hippocampal recordings. In Fig. 1b, the artifact is seen on the right side. Once we correctly identified the lead break artifact, we were also able to recognize the same artifact on earlier recordings, i.e. 3/1/2009. The results indicate a delay of one month between stopping adequate neurostimulation and increase of seizure frequency. In the patient's medical history, we did not identify any major traumatic injury which could have explained the lead fracture, although it must be emphasized that the patient was a farmer who performed heavy labor on a daily basis.

This case report illustrates several important aspects in the clinical follow up of patients treated with the RNS[®] System. First of all, if seizure frequency increases in an unexpected way, a lead break needs to be considered. Secondly, CT scan of the brain or standard radiography of the skull is not a sensitive tool to identify a lead break and therefore, surgical exploration of the lead may be required when there is a high degree of suspicion. Thirdly, lead impedance measurements and ICEEG recordings can help the clinician to monitor lead integrity and a change in lead impedance could be a marker of impending lead fracture. Early recognition of a lead break can result in an earlier exploratory surgical lead revision and avoid an unexpected increase in seizure frequency in patients with refractory epilepsy.

The long-term study of outcome of patients with the RNS System reported 3.5% lead damage and 3.1% lead revisions (Bergey et al., 2015). In this study, no information is available on how the lead break was discovered and how this impacted the clinical follow-up. In our case, there was a time window of 4 weeks between the lead break (witnessed by the artifact on the ICEEG) and loss of therapeutic efficacy. This indicates that there is a potential safe period between lead break and occurrence of break-

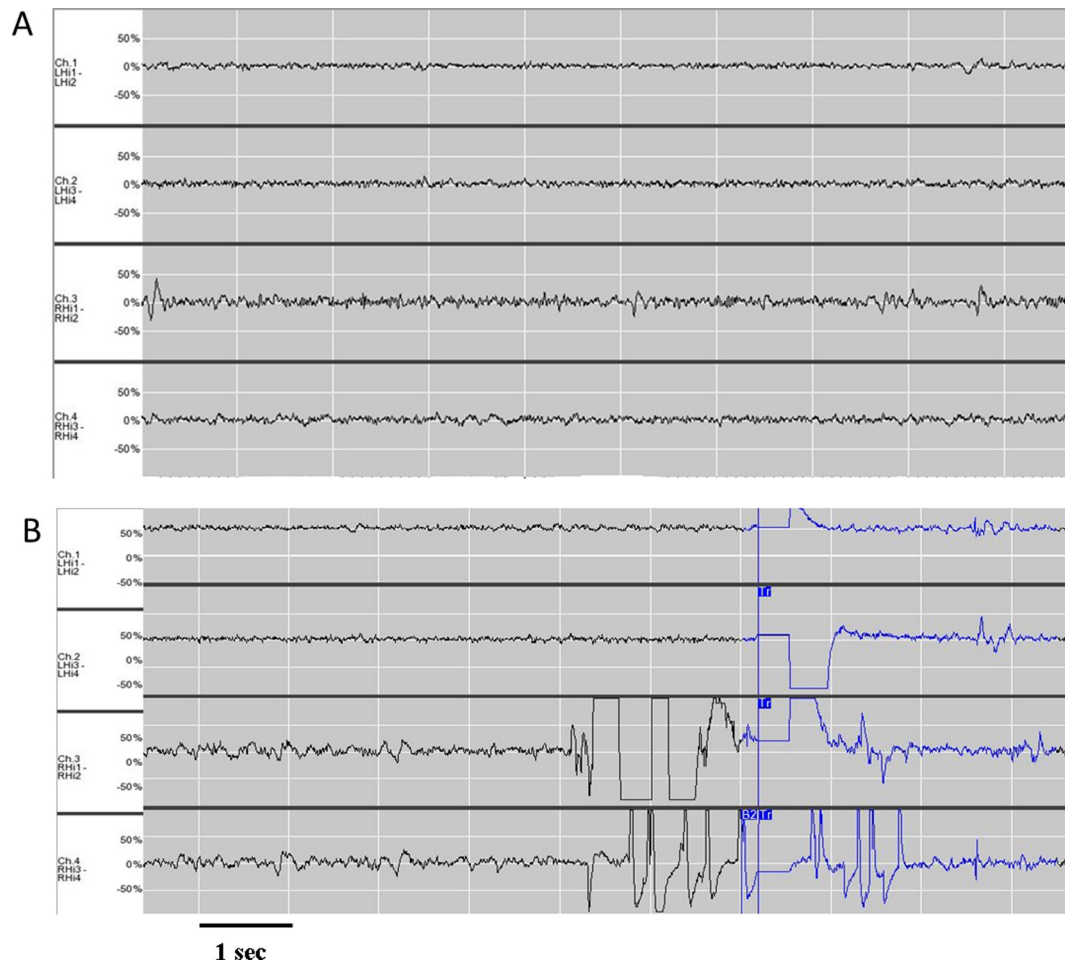


Fig. 1. (A, B) Analysis of the electrocorticograms. A: Normal interictal left (L1–4) and right (R1–4) hippocampal recordings. B: Lead-break artifact due to a broken wire in the lead making intermittent contact.

through seizures possibly due to the neuromodulatory effect of the treatment. This may be explained by neurostimulation induced changes in synaptic plasticity and neurogenesis (Lozano and Lipsman, 2013). A similar safe period was reported by Uthman in patients treated with vagus nerve stimulation (VNS) who encountered a lead break (Uthman et al., 1993).

To conclude, impedance monitoring of RNS ICEEG recordings can help clinicians in the early detection of lead fractures and prevent unexpected increase in seizure frequency in RNS implanted patients with refractory epilepsy.

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