Chronic ambulatory electrocorticography findings preceding sudden death in epilepsy

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Sudden unexpected death in epilepsy (SUDEP) is the leading cause of premature mortality in patients with refractory epilepsy, but the underlying mechanisms and the predictors of patient risk remain an active area of research.^{1,2} At present, risk assessment is based on disease severity accrued over the preceding years, but how the risk changes with therapy and disease progression have been poorly understood.³ To establish the pathophysiology of SUDEP, studies have capitalized on experimental models⁴ and rare terminal events recorded in the epilepsy monitoring unit.⁵ In these settings, the seizures are either induced or precipitated by weaning off medications and hence the electrophysiologic changes should be validated with spontaneous seizures recorded over longer time scale. Here we report progressive electrophysiologic changes in ambulatory electrocorticography preceding sudden death in a 38-year-old, right-handed woman who had intractable bitemporal epilepsy.

PRACTICAL IMPLICATIONS

Risk of sudden unexpected death in epilepsy increases with frequent generalized tonic-clonic seizures and response to therapy can be monitored with a responsive neurostimulation device.

Case report

A patient reported focal seizures with impaired awareness (2–4 every week) and generalized tonic-clonic seizures (1–2 every month) since she was 25 years old and her seizures remained refractory to multiple ($n = 8$) antiepileptic medications. There were no identifiable risk factors for epilepsy, and multiple 3T MRI scans revealed bitemporal asymmetric atrophy and hippocampal sclerosis (left worse than right). ¹⁸Fluoro-2-deoxyglucose (¹⁸F-FDG) PET imaging of the brain was consistent with bitemporal hypometabolism, and magnetic source imaging demonstrated frequent spikes localized over the right temporal pole and basal temporal regions. The patient underwent video scalp EEG investigation as a prelude to epilepsy surgery. The EEG confirmed frequent independent interictal epileptiform discharges over the bitemporal regions and 6 electroclinical seizures that emanated from the right ($n = 3$) and left ($n = 3$) anterior temporal regions. Neuropsychological evaluation suggested an increased risk of cognitive decline following resection of the right or left anterior temporal lobes. Based on these findings, in our multidisciplinary patient management conference, a consensus was reached to use a Food and Drug Administration–approved neuromodulation therapy, the RNS System (NeuroPace, Inc., Mountain View, CA), with 2 depth leads placed occipitally targeting the hippocampus bilaterally. The neurostimulator delivered electrical stimulation in response to electrographic seizures detected in the left or right hippocampi. In the first 6 months after activation of the neuromodulation therapy, the patient reported a decrease in seizure duration, although there was no change in clinical seizure frequency. In the subsequent months, her seizures increased in frequency even after up-titration of medications and stimulation therapy. Her antiseizure medications included carbamazepine, levetiracetam, clonazepam, and lacosamide. Analysis of her seizure diary revealed an increase in generalized convulsive seizures from 2 to 9 seizures per month over the last 4 weeks preceding the terminal event (figure 1). The patient reported a feeling of choking and gasping after some of the generalized seizures. There was a concomitant increase in the number of detections by the neurostimulator of events representative of the patient's electrographic seizures (figure 2). The terminal electrographic seizure (figure 3A) was

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Figure 1 Patient-reported seizures (focal and focal to bilateral tonic-clonic) after implantation of the RNS neurostimulator and leads

The x-axis represents months postimplantation and the y-axis represents seizures per month. Note the marked increase in generalized tonic-clonic (GTC) seizures at 20 months postimplantation.

recorded at 4:30 PM and demonstrated marked suppression of bihippocampal EEG in the postictal state that lasted until the end of the available recorded epoch, which was 60 seconds (figure 3B). The patient was found dead, prone on the bathroom floor with head turned laterally, tongue protruded and laterally bitten. The family declined an autopsy, and the coroner reported the cause of death as asphyxiation due to a seizure. We acknowledge the lack of autopsy report to confirm the cause of death and hence defined this as probable SUDEP.¹ The SUDEP risk inventory score (SUDEP-7) at the time of implantation was 4 and before death (19 months postimplantation) increased to 6.³

Discussion

The case study highlights 3 critical findings pertinent to SUDEP. First, among all the known risk factors of SUDEP, the strongest predictor is poor control of generalized tonic-clonic seizures (primary or secondary).¹ The chronic

ambulatory electrocorticography and seizure diary confirms this finding. There was an increase in generalized tonic-clonic seizures before the terminal event (figure 1). Second, postictal generalized EEG suppression is a potential direct or surrogate SUDEP biomarker although its reliability has been debated.⁶ Our patient had suppression of bihippocampal EEG following the terminal seizure. Due to the presence of limited spatial sampling, we are unable to determine if there was generalized EEG suppression preceding SUDEP. While treatment of seizures or prevention remains our priority, this case highlights the importance of developing novel treatment paradigms to stimulate arousal mechanisms in patients during postictal EEG suppression and its cardiorespiratory consequences as a potential life-saving strategy.⁷ Finally, risk assessment of SUDEP is a moving target, and the risk adjusts according to seizure burden. Chronic ambulatory electrocorticography allows us to quantify the seizure burden over a longer timescale, but automated methods may be developed to alert physicians about a substantial increase in electrographic seizures and in postictal electrographic suppression.

Figure 2 Long episodes (defined as events lasting greater than 30 seconds) from May 2016–June 2017

In this patient, long episodes were characteristic of electrographic seizures. Detection measures were modified to be more sensitive in November 2016, and this is reflected in the abrupt increase in long episodes in December 2016 and January 2017. However, since March 2017, there was a clear trend in increased long episodes (red horizontal line).

Figure 3 Terminal seizure followed by postictal EEG suppression

(A) Terminal seizure followed by (B) postictal EEG suppression recorded from the left and right hippocampi.

Author contributions

S. Pati: study concept and design, acquisition of data, data analysis and interpretation, critical revision of the manuscript for important intellectual content. L. Edwards: data analysis and interpretation, critical revision of the manuscript for important intellectual content. K. Riley: data acquisition. J. DeWolfe: data acquisition, critical revision of the manuscript for important intellectual content.

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