Seizure 21 (2012) 555–558

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Case report

Central apnea at complex partial seizure onset

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ARTICLE INFO

Article history:
Received 2 March 2012
Received in revised form 2 April 2012
Accepted 3 April 2012

Keywords:
Central apnea
SUDEP
Nocturnal seizures
Post-ictal cough

ABSTRACT

Sudden Unexpected Death in Epilepsy (SUDEP) is the most common cause of epilepsy related mortality in treatment resistant epilepsy. Most SUDEPs occur after one or more seizure(s) during sleep. Nocturnal seizures may go unrecognized. Respiratory depression in the peri-ictal period is one of the primary potential causes of SUDEP. Ictal and postictal apnea is often overlooked because it is not routinely assessed, but appears common and has been a recent focus of SUDEP research. We report a 37 year-old man who had central apnea as the initial manifestation of partial complex seizures associated with oxygen desaturation. This important pathophysiological consequence of a nocturnal complex seizure was identified by respiratory monitoring during a combined video EEG and sleep study. Diagnostic and therapeutic implications are discussed.

Sudden Unexpected Death in Epilepsy (SUDEP) is the most common cause of directly epilepsy-related death. Epidemiologic studies have identified multiple risk factors, including recent or frequent generalized tonic–clonic seizures (GTCS), antiepileptic drug (AED) polytherapy, duration of epilepsy, young age at onset, gender, and symptomatic etiology.[1] In many SUDEPs, patients die in their sleep and are found prone. Nocturnal seizures are independent risk factor for SUDEP.[2] The leading mechanisms of SUDEP include seizure-induced respiratory disorders, cerebral shutdown, and cardiac disorders.[3]

Our understanding of SUDEP is limited by the rarity of cases with multiple, simultaneously recorded physiological parameters. Cases witnessed in the community are usually preceded by a GTCS and observed to have a respiratory problem.[4] A summary of 13 cases of SUDEPs (8) and near-SUDEPs (5) in epilepsy-monitoring units showed GTCS preceded 12 cases and complex partial seizures (CPS) preceded one case.[3] Although none of these patients had respiratory effort or oximetry recorded, respiratory problems (postictal hypoventilation, apnea, cyanosis, inspiratory stridor, laryngospasm, pulmonary edema, or suffocation) were likely the primary cause in 8 patients. Cerebral shutdown with prolonged postictal EEG attenuation, ventricular fibrillation, and multiple mechanisms were considered likely causes in other cases.

We report a patient in whom two complex partial seizures (CPS) were recorded during combined polysomnography-video EEG. Both seizures occurred out of sleep and were associated with a central sleep apnea that progressed into an obstructive apnea when the seizure ended. Clinically this was followed by post-ictal cough.

1. Case report

A 37 year-old right-handed man began having CPS at age 3 years without an identified etiology. He had strong family history of epilepsy including childhood epilepsy in his father and paternal aunt and refractory epilepsy in his brother. He was started on anti epileptic drugs (AEDs) and seizures were fully controlled between ages 9 and 20 years. His CPS recurred at age 20 and increased in frequency over the next decade to 1–2 seizures per month occurring both during wakefulness and during sleep. His brain MRI was normal and ictal video EEG (VEEG) recording had previously revealed a right temporal focus. The patient was treated with oxcarbazepine (2700 mg/day; level 24 mg/dl) and phenobarbital (180 mg/day; level 18 mg/dl). He also took an estrogen supplement and spironolactone for a planned sex change.

At his last follow up visit, when asked about sleep, he reported one possible nocturnal seizure due to missed AEDs and an episode of sleepwalking and falling out of bed. He stated that this occurred when he was very stressed and happened once or twice a year. He had gained weight (BMI 32.4). A polysomnogram (PSG) with VEEG was obtained.

PSG showed an increased upper airway resistance syndrome and two CPS were captured. Each CPS was immediately preceded by a central hypopnea/apnea; these were the only two central respiratory events during the PSG. The first CPS occurred out of stage N1 in the supine position (Fig. 1) and was preceded by a respiratory event-related arousal and some movement. Nineteen

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http://dx.doi.org/10.1016/j.seizure.2012.04.001

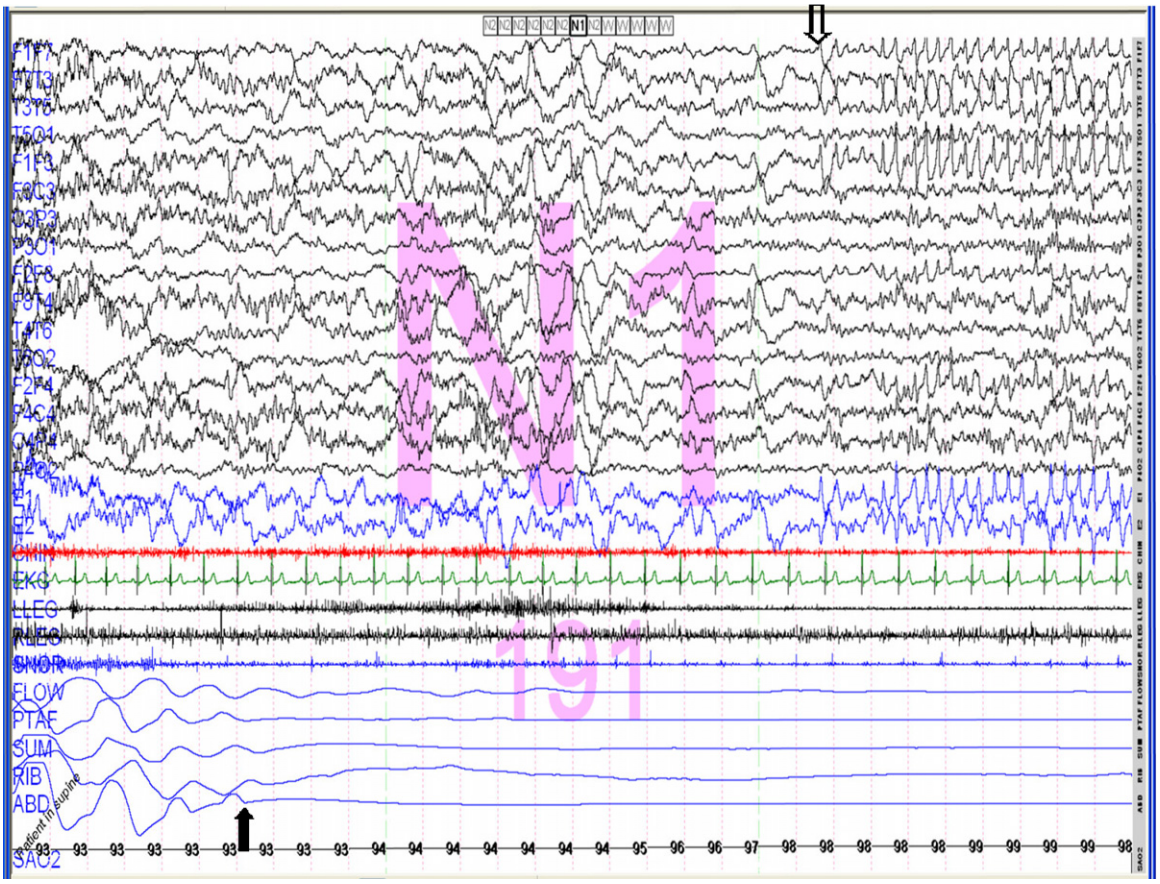

Fig. 1. Black arrow: Central apnea onset occurring out of expiration. Open arrow: Seizure onset over left temporal region.
Polysomnogram with Epilepsy Protocol using Care-fusion/Viasys acquisition system: Top 16 channels: (Black) EEG with longitudinal bipolar montage with following layout: Top 4 channels: Left temporal chain (Fp1-F7, F7-T3, T3-T5, T5-O1). Next 4 channels: Left parasagittal chain (Fp1-F3, F3-C3, C3-P3, P3-O1). Next 4 channels: Right temporal chain (Fp2-F8, F8-T4, T4-T6, T6-O2). Next 4 channels: Right parasagittal chain (Fp2-F4, F4-C4, C4-P4, P4-O2). Channels 17 and 18: (Blue) – Electroculogram. Top blue channel: Left eye. Bottom blue channel: Right eye. Channel 19: (Red) – Chin electromyogram. Channel 20: (Green) – Electrocardiogram. Channels 21 and 22: (Black) – Leg electromyogram. Top black channel: Left leg. Bottom black channel: Right leg. Channels 23: (Blue): Snore sensor. Channels 24–29: (Blue): Respiratory channels. Channel 24: Thermistor air flow. Channel 25: Pressure transducer air flow. Channel 26: Summation of the calibrated Respiratory Inductive Plethysomgraphy (RIP) signal of thoracic and abdominal effort. Channel 27: Thoracic RIP effort. Channel 28: Abdominal RIP effort. Channel 29: Oxygen saturation (SpO2). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

seconds prior to EEG seizure onset, there was a cessation of the abdominal and thoracic wall muscle activity and flattening of airway and pressure transducer signal, i.e. central apnea. Central nature of event was confirmed by respiratory inductance plethysmography and Konno mead loop recording. Central apnea lasted 27 s and was followed by an obstructive apnea pattern that lasted 26 s. Immediately after the obstructive event, the patient started coughing. There was an associated decrease in SaO_2 from 98 to 76 but no change in heart rate (from 68 bpm to 64 bpm) during the seizure.

The ictal EEG revealed seizure onset characterized by theta activity over left anterior temporal region lasting for 7 s, followed by delta slowing over the left hemisphere which spread to right temporal region. The video showed dystonic posturing of right upper extremity followed by him getting out of bed with his right arm postured and elevated. Shortly after, dystonia resolved and he started making the bed. The technician asked patient if he was okay. He coughed but did not respond and went back to sleep.

The second seizure occurred out of stage N2; he was on lying on his left side (Fig. 2). Eleven seconds before EEG seizure onset, there was a reduction of abdominal and thoracic wall movement as seen on sum effort channel along with reduction in airflow signal, i.e. central hypopnea. Simultaneous with EEG seizure onset, he had a central apnea lasting 54 s and terminating in obstructive event lasting for 26 s, and followed by coughing. SaO_2 dropped from 96 to 77 while heart rate was unchanged (60 bpm). EEG and clinical features were similar to the first seizure. The patient was unaware of either CPS in the morning.

2. Discussion

Our patient with temporal lobe epilepsy had two nocturnal CPS preceded by central hypopnea/apnea that evolved into obstructive apnea. These were the only two central hypopnea/apnea events during the PSG, and both were followed by a left temporal ictal discharge within 20 s. These apneas were most likely ictal and represent the first polygraphic and clinical manifestations of the seizure. Many factors determine the presence, distribution, and amplitude of ictal scalp activity, e.g. seizure focus location, depth, spatial distribution and orientation as well as spread pattern.[5] Thus, actual electrical seizure discharge may have preceded the central apnea but was not detected on scalp EEG yet. His ictal semiology and scalp EEG pattern are consistent with a mesial temporal seizure onset; scalp EEG changes from mesial temporal region may follow intracranially recorded seizure onset by more than 30 s or may never be detected on scalp EEG.[6]

In humans, respiratory arrest can be induced by electrical stimulation of the amygdala during the expiratory phase of the respiratory cycle when pulmonary stretch receptor activity is attenuated.[7,8] In our patient both seizures with left temporal lobe

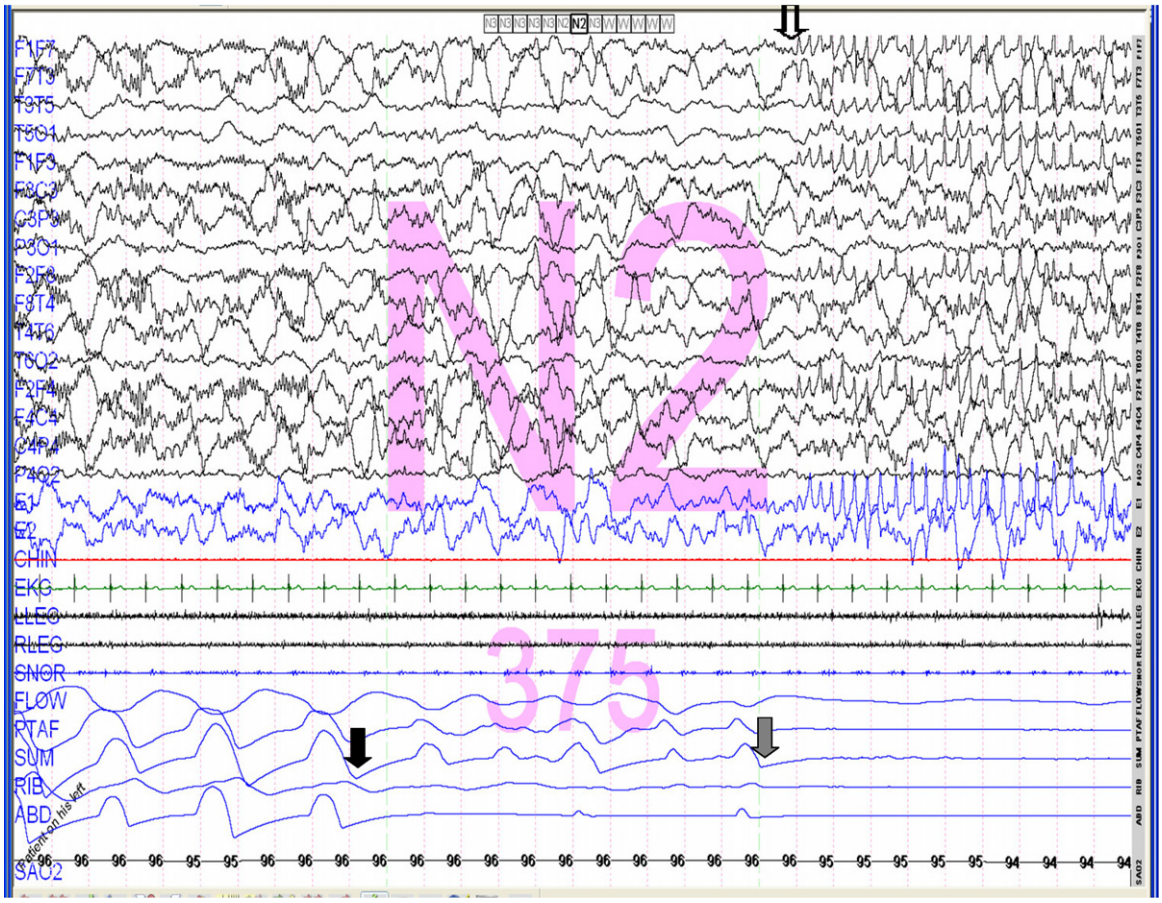

Fig. 2. Black arrow: Onset of central hypopnea occurring out of expiration as seen on sum channel. Grey arrow: Central apnea onset. Open arrow: Seizure onset over left temporal region.
Polysomnogram with Epilepsy Protocol using Care-fusion/Viasys acquisition system: Top 16 channels: (Black) EEG with longitudinal bipolar montage with following layout: Top 4 channels: Left temporal chain (Fp1-F7, F7-T3, T3-T5, T5-O1). Next 4 channels: Left parasagittal chain (Fp1-F3, F3-C3, C3-P3, P3-O1). Next 4 channels: Right temporal chain (Fp2-F8, F8-T4, T4-T6, T6-O2). Next 4 channels: Right parasagittal chain (Fp2-F4, F4-C4, C4-P4, P4-O2). Channels 17 and 18: (Blue) – Electroculogram. Top blue channel: Left eye. Bottom blue channel: Right eye. Channel 19: (Red) – Chin electromyogram. Channel 20: (Green) – Electrocardiogram. Channels 21 and 22: (Black) – Leg electromyogram. Top black channel: Left leg. Bottom black channel: Right leg. Channels 23: (Blue): Snore sensor. Channels 24–29: (Blue): Respiratory channels. Channel 24: Thermistor air flow. Channel 25: Pressure transducer air flow. Channel 26: Summation of the calibrated Respiratory Inductive Plethysomgraphy (RIP) signal of thoracic and abdominal effort. Channel 27: Thoracic RIP effort. Channel 28: Abdominal RIP effort. Channel 29: Oxygen saturation (SpO2). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

onset, showed stereotypical central respiratory events that began out of the expiratory phase and were associated with significant oxygen desaturation. The respiratory rhythm is generated in the rostral ventrolateral medulla.[9] Inputs to this area descend from insular cortex, hypothalamus and reticular formation. Seizures arising in or spreading to these brain regions may inhibit medullary respirator centers. In one series of TLE patients undergoing invasive EEG monitoring, ictal apneas were associated with contralateral seizure spread suggesting that both temporal lobes are involved in respiratory control.[10] However our patient had central apnea associated with EEG seizure changes seen unilaterally over left temporal region.

An alternative explanation for the patient's seizure-related apnea is that the respiratory dysfunction preceded and possibly triggered the seizure. Brief apnea is not known to provoke seizures. More often, hyperventilation is a provocation. Further, if seizures were triggered by apnea and hypoxia then diffuse EEG changes would be expected but were not seen in our case.

Seizure-related central respiratory dysfunction is probably more common than it is recognized and may be a risk factor for SUDEP. Central apnea and ictal hypoxemia occur during CPS.[11] Our patient had central apnea as the likely initial manifestation of nocturnal left temporal seizures. The respiratory system is more vulnerable during sleep and nocturnal seizures may cause greater disruption of central respiratory dysfunction than diurnal seizures in some patients. If severe and prolonged, peri-ictal central respiratory dysfunction could lead to death as observed in several cases of SUDEP or near-SUDEP recorded in epilepsy monitoring units.[3] Additional comorbidities such as obesity or obstructive sleep apnea could exacerbate seizure-related respiratory dysfunction but their role as SUDEP risk factors have not been studied. Additional studies are needed to understand the relationship between seizure-related respiratory changes and SUDEP risk. Finally, the concurrence of apnea/hypopnea in our patient's seizures and postictal cough could be coincidental, but it would be valuable to study a series of patients with postictal cough to see if it is associated with ictal respiratory disorders.

Our case also highlights the deficiencies of self-reporting of seizure activity. Our patient denied having seizures but his sleep/video EEG revealed two nocturnal CPS that he was unaware of. Thus patient was clinically considered "seizure free" in his medical chart prior to the sleep study. Asking about sleep pattern and sleep disorders and obtaining combined sleep/video EEG studies may help identify patients with ictal-induced central respiratory suppression.

References

1. Hesdorffer D, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. *Epilepsia* 2011;**52**:1150–9.
2. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at high risk. *Epilepsia* 2012;**53**(2):253–7.
3. Devinsky O. Current concepts: Sudden Unexpected Death in Epilepsy. *NEJM* 2011;**365**:1801–9.
4. Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. *Journal of Neurology Neurosurgery and Psychiatry* 2000;**68**:211–3.
5. Hashiguchi K, Morioka T, Yoshida F, Miyagi Y, Nagata S, Sakata A, et al. Correlation between scalp recorded electroencephalographic and electrocorticographic activities during ictal period. *Seizure* 2007;**16**(3):238–47.
6. Ebersole JS, Pacia SV. Localization of temporal lobe foci by ictal EEG patterns. *Epilepsia* 1996;**37**(4):386–99.
7. Kaada BR, Jasper H. Respiratory responses to stimulation of temporal pole, insula, and hippocampal and limbic gyri in man. *AMA Archives of Neurology and Psychiatry* 1952;**68**(5):609–19.
8. Nelson DA, Ray CD. Respiratory arrest from seizure discharges in limbic system. *Archives of Neurology* 1968;**19**(2):199–207.
9. Barnes BJ, Tuong CM, Mellen NM. Functional imaging reveals respiratory network activity during hypoxic and opioid challenge in the neonate rat tilted sagittal slab preparation. *Journal of Neurophysiology* 2007;**97**:2283–92.
10. Seyal M, Bateman LM. Ictal apnea linked to contralateral spread of temporal lobe seizures; Intracranial EEG recordings in refractory temporal lobe. *Epilepsia* 2009;**50**(12):2557–62.
11. Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain* 2008;**131**:3239–45.