Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP)

In "Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP)", Vilella et al. found that in a cohort of patients with intractable generalized or focal epilepsy, 22% of seizures were followed by postconvulsive central apnea (PCCA), defined as ≥1 missed breath without any other explanation; one of these patients died of probable SUDEP, suggesting that the incidence of SUDEP is 5.1 per 1,000 patient-years. They concluded that PCCA may be a clinical biomarker for SUDEP. Pursuant to these findings, Rose et al. report a case of SUDEP in a patient with PCCA; however, they comment that although PCCA may be associated with SUDEP, they suspect that it is not a requirement for SUDEP, given that there is a known relationship between SUDEP and prone positioning (which can lead to obstructive apnea). They also question the proposed incidence rate of SUDEP, as it was based on only 1 death. Dasheiff notes that (1) it is not possible to distinguish between PCCA and central sleep apnea without advanced instrumentation, and (2) a threshold higher than 1 missed breath should be used to define PCCA. Vilella et al. respond that (1) the true incidence of PCCA and SUDEP, both individually and separately, is, indeed, unknown; (2) there may be a multitude of risk factors for SUDEP, including both prone positioning and PCCA; and (3) using a higher bar to define PCCA would, actually, better illustrate the relationship between PCCA and SUDEP in this series. Further research on the risk factors and incidence of SUDEP is needed.

Ariane Lewis, MD, and Steven Galetta, MD
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Reader response: Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP)

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We read with interest the study by Villella et al., which suggested postconvulsive central apnea (PCCA) with asystole as a biomarker for sudden unexpected death in epilepsy (SUDEP).[1] We encountered a similar case of a 28-year-old man with intractable temporal lobe epilepsy who had a cluster of 3 generalized convulsive seizures with postictal generalized EEG suppression during invasive monitoring. He had PCCA with asystole after the third seizure and was resuscitated in hospital, but died of probable SUDEP during follow-up.

It remains uncertain what fraction of SUDEP cases are associated with PCCA. The reported incidence of 5.1 per 1,000 patient-years is similar to that found for severe intractable epilepsy,[2] but is based on the probable SUDEP of only 1 patient. PCCA may not be a requirement for the majority of SUDEP cases because it would not produce the known correlation with prone position during sleep (with its associated risk for obstructive apnea) and, except in the hospital setting where intubation and advanced resuscitation is possible, would not depend on whether the event was witnessed.[3–5] It is more likely that PCCA contributes to SUDEP in patients for whom obstructive apnea is not a major concern.

Author disclosures are available upon request (journal@neurology.org).

1. Vilella L, Lacuey N, Hampson JP, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). Neurology 2019;92:e171–e182.
2. Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: a review of incidence and risk factors. Epilepsia 2005;46(suppl 11):54–61.
3. Liebenthal JA, Wu S, Rose S, Ebersole JS, Tao JX. Association of prone position with sudden unexpected death in epilepsy. Neurology 2015;84:703–709.
4. Sveinsson O, Andersson T, Carlsson S, Tomson T. Circumstances of SUDEP: a nationwide population-based case series. Epilepsia 2018;59:1074–1082.
5. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013;12:966–977.

Reader response: Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP)

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It is generally thought, although probably not scientifically proven, that convulsive ictal apnea is secondary to diaphragm tonic contraction in conjunction with tonic limb muscular contraction. Clonus of limbs and diaphragm are also likely to impair respiration. Postictal apnea is a common occurrence, and patients are also generally atonic during the initial period. Conversely, central sleep apnea occurs in a different setting, can be both REM and non-REM, and unlikely linked to motor activity. Thus, trying to identify the mechanisms associated with "central" apnea after seizure would require full instrumentation of all pertinent variables, which was not done in this study.[1] Furthermore, missing a single breath to define apnea is a low bar.

1. Vilella L, Lacuey N, Hampson JP, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). Neurology 2019;92:e171–e182.

Author response: Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP)

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We sincerely appreciate the comments of Rose et al. and their valuable contribution in reporting a clinical case with a fatal/near-fatal phenomenology similar to our cases.[1] We believe that this emphasizes the role of postconvulsive central apnea (PCCA) as a potential sudden unexpected death in epilepsy (SUDEP) biomarker. We completely agree that the true incidence of PCCA in patients with SUDEP is unknown because most of them occur in nonmonitored settings. Moreover, current knowledge suggests that SUDEP may be a heterogeneous phenomenon, and prone position during sleep may be a contributor in some. However, in our reported cases,[1] PCCA did not occur concurrently with the prone position, as can be appreciated in the videos provided, and PCCA is an observation common to several animal models and human series of SUDEP and near SUDEP.[2,3]

We appreciate Dr. Dasheiff's comments on our article, as well.[1] We agree that it is likely that apnea, during the generalized tonic-clonic phase, is due to diaphragm tonic contraction with the following clonus of the limbs and diaphragm contributing to breathing dysfunction. A central apneic component may also be concurrent, although this is difficult to prove. To our knowledge, the true incidence of PCCA has not been previously established, although it is a common feature in animal models and human series of near SUDEP and SUDEP.[2,3] The presence of a dense muscle artifact in the EEG leads after a generalized convulsive seizure suggests that muscle tone is present, rather than patients being purely atonic.[1,4] The presence of muscle

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artifact was not related to PCCA or laryngospasm.[1] We agree that a single breath to define apnea is a low threshold compared with standard sleep studies, although the standard definition would actually further highlight the relative rarity of this phenomenon. Even if brief, as in our SUDEP case,[1] it could be a sensitive predictor of transitory breathing dysfunction posing the patient to a greater risk of SUDEP. Prolonged PCCA with bradycardia/asystole may pose greatest risk. Further prospective studies are needed to validate this hypothesis.

1. Vilella L, Lacuey N, Hampson JP, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). Neurology 2019;92:e171–e182.
2. Johnston SC, Siedenberg R, Min JK, Jerome EH, Laxer KD. Central apnea and acute cardiac ischemia in a sheep model of epileptic sudden death. Ann Neurol 1997;42:588–594.
3. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013;12:966–977.
4. Gastaut H, Broughton RJ. Epileptic Seizures. Clinical and Electrographic Features, Diagnosis and Treatment. Springfield: Charles C Thomas; 1972.

CORRECTION

Psychiatric disorders in C9orf72 kindreds

Study of 1,414 family members

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In the article "Psychiatric disorders in C9orf72 kindreds: Study of 1,414 family members" by Devenney et al.,[1] table 1 incorrectly repeats C9orf72 positive and C9orf72 negative values in the FTD and ALS columns. Also, the *p* values in the last row are incorrect. The corrected table appears below. The authors regret the error.

Reference

1. Devenney EM, Ahmed RM, Halliday G, Piguet O, Kiernan MC, Hodges JR. Psychiatric disorders in C9orf72 kindreds: study of 1,414 family members. Neurology 2018;91:e1498–e1507.

Table 1 Demographic data for probands and relatives according to *C9orf72* status and diagnosis

	All Probands (n = 89)	*C9orf72* carriers (n = 29)	*C9orf72* noncarriers (n = 60)	Carriers vs noncarriers, *p* value	FTD (n = 46)	ALS (n = 43)	FTD vs ALS, *p* value
No. of relatives (N)	1,414	463	951	—	751	663	—
First-degree relatives (N)	663	237	426	—	382	281	—
Second-degree relatives (N)	751	226	525	—	369	382	—
Relatives age in years (SD)	—	49.7 (24.3)	51.5 (25.3)	0.20	49.9 (25.7)	51.9 (24.3)	0.12
Relatives sex (female:male)	—	228:235	483:468	0.20	378:373	333:330	0.65

Abbreviations: ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia.

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