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EDITORIAL

Challenges in Decoding Sudden Unexpected Death in Epilepsy: The Intersection Between Heart and Brain in Epilepsy

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Patients with epilepsy are at least 2- to 3-fold higher risk for dying prematurely and suddenly than the general population.[1–3] When an unexpected, nontraumatic and nondrowning death occurs suddenly in individuals with epilepsy (excluding status epilepticus), in which postmortem examination does not reveal a toxicologic or anatomic cause of death, the term sudden unexpected death in epilepsy (SUDEP) is used.[4] SUDEP is one of the most frequent causes of death among patients with drug-resistant epilepsy (cumulative lifetime risk estimated 35%)[5,6] and ranks second only to stroke among neurological conditions in the United States in terms of potential years of life lost.[2] The annual incidence of SUDEP is estimated to be 1.16 cases for every 1000 patients with epilepsy, in contrast to sudden unexplained death syndrome (SUDS), which is estimated to occur in 0.5 cases for every 1000 individuals per year in the general population.[5,7]

See Article by Chahal et al.

The pathophysiology of SUDEP is heterogeneous, likely involving cardiac, autonomic, respiratory, and polygenic contributors.[8] Most SUDEP cases occur at night or during sleep when the death is not witnessed, leaving many questions unanswered. The major risk factor for SUDEP is the occurrence of generalized tonic-clonic and nocturnal seizures. The lack of treatment with antiepileptic drugs or subtherapeutic levels of such drugs, nonadherence to treatment regimens, and frequent changes in regimens are additional risk factors for SUDEP.[9] It has been demonstrated that chronic epilepsy may result in hypoxemia and catecholaminergic surges and consequent cardiac and vascular damage, which may contribute to electrical and mechanical dysfunction.[10,11] In some individuals, the lethal trigger might be ictally induced prolonged hypoxemia and hypercapnia resulting in acidosis that predisposes to bradycardia or asystole, whereas in others, it may be a malignant cardiac arrhythmia initiated ictally or via an interictal epileptiform activity.[12] Interestingly, although ictal bradycardia/asystole is thought to play a critical role in SUDEP pathophysiology, most SUDS cases attributed to genetically mediated cardiac diseases develop secondary to ventricular tachyarrhythmias, a distinction in the mechanism of cardiac arrest/death between the 2 conditions. Hence, SUDEP may be the consequence of the epileptic seizures itself, in addition to possible direct contribution of pathogenic variants in genes encoding myocardial

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proteins/channels. In fact, there might be at least 2 distinct clusters of patients with epilepsy at high risk for SUDEP: a younger group with no known comorbidities and infrequent seizures who may host pathogenic variants in primary arrhythmia syndrome genes and an older population with polygenic predisposition, polymedication, and treatment-refractory severe seizures.[13] Currently, there are limited measures to prevent SUDEP. Because a tonic–clonic seizure precedes most SUDEP cases, seizure control with appropriate medication use and counseling on lifestyle is the focus of prevention (reviewed in detail by Devinsky).[9]

Although the genetic underpinnings of SUDEP are yet to be fully defined, the list of candidate SUDEP genes has been growing rapidly, and discoveries have been facilitated by progress in the field of sudden cardiac death and sudden infant death syndrome and by insights from experimental animal models.[13] Data suggest that a pathogenic variant in dominant epilepsy genes is found in up to a quarter of SUDEP cases.[14] Most of these variants are established causes of treatment-resistant epilepsy and associated with frequent generalized tonic-clonic seizures, for example, *SCN1A*, *SCN8A*, and *DEPDC5*.[13] An additional 7% to 10% of cases have a clinically relevant pathogenic variant in cardiac arrhythmia genes, indicating that these cases may be SUDS cases.[15,16] Familial SUDEP cases are, however, rare,[17] indicating that genetics might be just one of the contributors to SUDEP pathogenesis. A baseline cardiac evaluation with an ECG may be useful in SUDEP families. Despite the considerable efforts in this area, the complex mechanisms and circumstances surrounding SUDEP remain insufficiently investigated for several reasons, including its relatively low incidence, its unpredictable occurrence often in unwitnessed settings, its low rate of complete autopsy examinations, and the paucity of analytically useful postmortem material for genetic testing.[4]

In this issue of the *Journal of the American Heart Association (JAHA)*, Chahal and colleagues[18] report on the largest single-center cohort of SUDEP cases described to date, with whole-exome sequencing genetic testing performed for cases with DNA available. This is the result of an extraordinary effort of systematic creation and adjudication of cases to build a registry of sudden death. After multisource identification of over 13 000 cases of sudden cardiac death, SUDS, sudden infant death syndrome, and out-of-hospital cardiac arrest occurring between 1960 and 2016 in individuals aged 0 to 90 years, the authors identified 368 cases meeting the diagnosis of epilepsy. Subsequently, by cardiac pathologist input, they reevaluated and reclassified these cases as *non-SUDEP*, when there was clearly an alternative cause of death such as trauma, drowning, drug overdose, suicide, or homicide, or as *SUDEP* (with subcategories) according to the unified SUDEP definition and classification.[4] Of the 368 cases, 58 were classified as non-SUDEP and 96 as SUDEP cases; the remaining 214 cases (66%) had only death certificate data and insufficient records for cause of death ascertainment. The age of death in SUDEP decedents spanned from 1 to 84 years. With a mean age of 37 years at death, these individuals were on average 15 years younger than the non-SUDEP decedents. Only 16% of SUDEP decedents had an antemortem ECG performed, leaving a potential overlap with manifest inherited arrhythmia syndromes not excluded in most cases. Although autopsy was performed in 83/96 (86%) SUDEP cases, only 34 (41%) underwent neuropathological examination. Further, cardiac pathology examination was performed in only 13 (16%), resulting in incomplete records regarding critical pathological findings, such as coronary artery origin and presence/extent of coronary atherosclerosis. Among SUDEP cases, there were 5 individuals with antemortem diagnosis of Dravet syndrome, an infantile-onset intractable epilepsy caused by heterozygous loss-of-function mutations in the *SCN1A* gene, which encodes brain type-I voltage-gated sodium channel $Na_V1.1$. Considering a dominant inheritance model, whole-exome sequencing and subsequent analysis of variants in 166 sudden death-susceptibility genes identified 18 ultra-rare nonsynonymous variants of uncertain significance in 6 out of 11 individuals, in whom genetic material was available for testing, with all 6 cases hosting multiple variants. One of the 6 decedents carried an additional homozygous variant in the *CLCN2* gene, which encodes the voltage-gated chloride channel 2. Four transcript variants encoding different isoforms have been reported for this gene. Pathogenic variants in this gene have been implicated in leukoencephalopathy (autosomal recessive)[19] and familial hyperaldosteronism type I (autosomal dominant)[20]; whether heterozygous pathogenic variants can cause idiopathic generalized epilepsy is currently unclear and remains to be investigated.[21,22]

The work of Chahal et al[18] highlights many aspects of the current situation of clinical care of people with epilepsy and SUDEP research. First, it underscores the central role of interdisciplinary investigation and care of patients with epilepsy at high risk for SUDEP. To this end, minimal cardiac evaluation in patients with epilepsy should include a detailed history of cardiac events, family history of sudden infant death syndrome, SUDS, or SUDEP, and an ECG, allowing the documentation of manifest primary arrhythmia syndromes, such as long QT syndrome and Brugada syndrome. It should, however, be noted that a single ECG cannot rule out a concealed primary arrhythmia syndrome, as first manifestation of both conditions in the presence of disease-specific triggers, such as

hypokalemia and medication intake in long QT syndrome and fever in Brugada syndrome, is not rare.[15] A minimal suspicion of a concomitant cardiac condition should, therefore, warrant cardiologic reevaluation in those with epilepsy. Second, Chahal et al demonstrate the gaps in the current specialist-pathological examination of SUDEP cases and once again underscore the key role of the ascertainment of cause of death in decedents with epilepsy. Incidental autopsy findings of uncertain significance are common in decedents both with and without epilepsy and may result in erroneous interpretations and misdiagnosis when not evaluated properly by specialist cardiac and neuropathologists.[23,24] Finally, the results of this study show that biological material for genetic testing are often not stored for SUDEP cases, and family history may often not be available at autopsy. Careful review of the family history in SUDEP cases is, however, critical to identify potential familial cardiac and neurological conditions, and any concern should result in a molecular genetics study.[13]

In summary, SUDEP continues to be an area of active research with the goal of identifying at-risk individuals and decreasing its incidence. The major lesson from the study by Chahal and colleagues is that SUDEP is underinvestigated even in most advanced centers providing advanced cardiovascular, neurological, and pathological services. Strengthening existing interdisciplinary collaboration is necessary to provide optimal care to patients with epilepsy, in particular, to identify and manage modifiable risk factors for SUDEP and reassure those at substantially low risk. Building international and multidisciplinary consortia that would investigate the causes, mechanisms, and circumstances of SUDEP is of paramount importance to the long-term care of people with epilepsy and prevention of tragic fatalities.

ARTICLE INFORMATION

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Disclosures

None.

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