

Sudden death in epilepsy

Where is the “heart” of the problem?

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Every year, 5,000 people with epilepsy die of sudden unexpected death (SUDEP) in the United States alone, a reflection of a 20-fold increased risk of this devastating complication compared to the general population.¹ Patients with uncontrolled seizures are particularly vulnerable. So, our knee-jerk reaction as neurologists trying to understand SUDEP has been to investigate various theories of how seizures can cause sudden death: after all, patients with epilepsy are dying, so of course the brain must be at the heart of the problem. Tremendous past and ongoing efforts have investigated various potential seizure-related consequences that may compromise cardiac and respiratory function, including sympathetic hyperactivation, parasympathetic suppression² or overdrive,³ abnormal heart rate variability, and respiratory suppression.⁴ A new study published in this issue of *Neurology*®,⁵ led by neurologists and cardiologists, took a population-based approach and asked the question slightly differently, providing a broader perspective.

Drawing from one national registry cataloging persons with cardiac arrest and another documenting outpatients with epilepsy, the Lamberts et al. investigators defined cases as patients with epilepsy who experienced ventricular tachycardia/fibrillation (VT/VF). These patients had a higher prevalence of congenital/herited heart disease (17% vs 1%, $p = 0.002$) and were younger when experiencing VT/VF (57 vs 64 years, $p = 0.023$) as compared to a control cohort of nonepileptic VT/VF patients. Conversely, these cases had a higher prevalence of clinically relevant heart disease when compared to epilepsy controls without VT/VF. Synthesizing these results, the main take-home messages are that (1) cardiovascular disease rather than epilepsy characteristics is the strongest risk factor for VT/VF in epilepsy and (2) having epilepsy seems to be linked with a higher risk of cardiovascular disease. The implications require some attention.

Let's consider for a moment that seizures are not the only driver leading to sudden death in patients with epilepsy. We accept the idea that patients with epilepsy have more seizures than the general population because they have an inherent structural/genetic/functional/acquired

dysfunction in the electrophysiologic networks within their brain. Let us hypothetically entertain the idea that similarly, they have more sudden cardiac arrests because they have an inherent structural/genetic/functional/acquired dysfunction in the electrophysiologic networks within the heart. Pursuing this line of thought actually allows us to see several supportive pieces of evidence. The genetic epilepsy syndromes, ranging from the disorders of metabolism to mitochondrial disorders, often lead to abnormal deposits in the brain and the heart, and disrupt the energy needs of multiple organ systems, including the brain and the heart. A logical assumption with channelopathies is that they should in fact affect multiple organs where these channels are vital, rather than either the heart or the brain: prolonged QT syndrome is an obvious example where recent and old data have demonstrated a link between a classical cardiac channelopathy and epilepsy.^{6,7} Stroke—a leading cause of acquired epilepsy—and myocardial infarction actually result from the same risk factors in an older patient group, while the psychosocial implications of uncontrolled epilepsy ranging from reduced levels of activity, depression, and lower income could hypothetically lead to a lifestyle that is not ideal from a cardiac health perspective for any age group. The examples of such parallels between brain health and cardiac health abound once the alternative hypothesis door is open, as it was with Lamberts and colleagues.

The study at hand⁵ has several limitations. Two different registries with different methods of defining epilepsy were used, introducing the potential for ascertainment bias. The cardiac arrhythmia analyzed was limited to VT/VF, so the applicability of the study's findings to other cardiac rhythms that may lead to sudden cardiac death in epilepsy remains unclear. The analysis of this subject is further complicated when we attempt to draw a line between sudden cardiac arrest and SUDEP based on stringent autopsy findings. Of the 18 cases, 8 had an identifiable acute cardiac cause of death. One death was attributed to acute pulmonary disease. In 5, a cardiac

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cause was assumed, either on the basis of recent chest pain or preexisting cardiac disease, but autopsy was not performed. Of the remaining 5 patients, 3 patients with hypertrophic cardiomyopathy, drug-induced QTc prolongation, and transient cardiac ischemia were not considered SUDEP according to Nashef or Annegers criteria from 1997.^{8,9} This left only 2 cases classifiable as (near) SUDEP. The study illustrates that the inclusive definition of sudden cardiac arrest and our exclusive definition of SUDEP likely neglect a mechanism of sudden death requiring the coexistence of cardiac disease and recurrent seizures, supporting the concept of SUDEP plus.¹⁰

Should we then consider that the heart may at least sometimes be at the heart of the problem of sudden death in patients with epilepsy? The data speak for themselves: if hard numbers are any guide, only 2 of the 18 epilepsy patients who had sudden death in the cohort reported by Lambert et al. actually fulfilled the criteria for SUDEP. This may be a definition problem, as alluded to above, but it may also reflect the magnitude of cardiac pathology in patients with epilepsy. Of course, we may say that cardiac pathology seen in autopsies of SUDEP patients reflect the deleterious sympathetic effects of seizures, and that cardiac pathology in patients with epilepsy is mainly the result of seizures. Either we neurologists continue to focus exclusively on preventing and treating seizures, or we pay more attention to cardiovascular risk factors in people with epilepsy to reduce the rate of sudden death in this population. Either or both: the choice is ours.

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Lara Jehi, MD: drafting the manuscript for intellectual content. Stephan Schuele, MD, MPH: revising the manuscript for intellectual content.

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