

Genes cut across systems

Neurologists should think “heart” and cardiologists “brain”

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Despite a strong association with a history of uncontrolled convulsions, until recently, mystery surrounded sudden unexpected death in epilepsy (SUDEP). This is when a person with epilepsy, usually a young adult, dies suddenly without a structural or toxicologic cause for death identified.¹ The Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) has partially dispelled this mystery. Deaths occurred, in the absence of timely assistance, in the aftermath of a convulsion with postictal, centrally mediated severe respiratory and cardiac dysfunction. Hypoventilation and bradyarrhythmias were seen, with asystole usually occurring after apnea.² Much has been made of respiratory compromise in the context of postictal coma, usually in the setting of generalized EEG suppression, when the individual has impaired ability to improve oxygenation by correcting position or enhancing respiration despite hypercapnia and hypoxia.³ This observation ties in with conclusions of a recent review of arrhythmias and seizures that found that postictal arrhythmias mostly occurred following convulsions and often correlated with (near) SUDEP.⁴ The MORTEMUS study showed a clear interrelation between respiratory and cardiac dysfunction.³

Genetic predisposition, particularly, but not exclusively, to sudden cardiac death, has long seemed plausible as a contributor in at least some SUDEP cases. Such predisposition not only accounts for disorders such as long QT syndrome (LQTS), with sudden death presenting as early as in utero, but also some acquired disorders. Cardiac arrest following a first ST elevation myocardial infarction, for example, is more common with a family history of sudden cardiac death, and genetic susceptibility is implicated in drug-induced long QT.⁵ A previous review explored the potential of coexisting genetic liability to cardiac arrhythmias as a factor in SUDEP, but lacked bridging clinical evidence between cardiac inherited gene determinants and SUDEP.⁶ Recent studies have begun to fill that gap, although more evidence is needed.

In an Australian coronial study of 68 SUDEP cases, researchers identified previously reported amino acid changing variants in the 3 most common

LQTS genes (*LQTS1*, *KCNQ1* [*KV7.1*]; *LQTS2*, *KCNH2* [*HERG/KV11.1*]; *LQTS3*, *SCN5A* [*NaV1.5*]) in 6 (13%) cases, 2 in *KCNH2* and 4 *SCN5A*.⁷ More recently, the group investigated 61 SUDEP cases.⁸ They performed exome-based analysis of rare variants and screened cardiac arrhythmia, respiratory control, and epilepsy genes for variants predicted to be pathogenic with a frequency of <0.1%. They found variants in 28 of the 61 (46%), including known LQTS mutations in 4 (7%) and candidate variants in genes potentially predisposing to cardiac arrhythmia in 9 (15%), with 1 mutation each in *SCN5A* and *KCNQ1*, and 2 mutations and 1 candidate variant in *KCNH2*. Fifteen (25%) also had mutations in known epilepsy genes, 6 in *DEPDC5*. This study thus showed that a sizeable proportion of SUDEP cases had relevant mutations in cardiac arrhythmia and epilepsy genes. A comparator group of people with epilepsy in a similar age group dying of other causes would be of interest.

In this issue of *Neurology*®, Auerbach et al.⁹ report on seizures, arrhythmias, and biomarkers using their LQTS Registry in a large cohort of 965 genetically confirmed LQTS cases (LQTS[+]) comparing them to those without genetic LQTS (LQTS[−]). This follows from an earlier smaller study reporting more frequently reported seizures in LQTS2 than other LQTS subtypes.¹⁰ Compared to LQTS(−), in the current study, more LQTS1, LQTS2, and LQTS(+) participants were classified as having seizures. In LQTS(+) cases, a strong positive correlation was found between QTc duration and seizure history. Genotype influenced clinical presentation. LQTS2 mutations in the *KCNH2* pore domain positively predicted both arrhythmias and seizures, while mutations in the cyclic nucleotide binding domain conferred a negative risk of seizures, but not arrhythmias. LQTS2 and sex also both predicted seizures independently. A history of seizures was the strongest independent predictor of arrhythmias.

This study adds important observations on the relationship between seizures and LQTS and potential overlap between genetic cardiac arrhythmias and epilepsy. Seizure manifestation, however, may still

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have been a reflection of more severe arrhythmias rather than epilepsy. The authors defined a seizure history as a personal history of seizures or epilepsy or antiseizure medication. Epilepsy phenotyping relied on self or physician reporting and not on systemic ascertainment. The correlation between seizure history and arrhythmias may be explained by genetic factors causing both cardiac disease and epilepsy but may also reflect a misdiagnosis of epilepsy. β -Blockers, however, reduced the risk of arrhythmias in genotype-positive cases but not seizure risk. This and the differing associations between genotypes and seizure risk strongly argue in favor of neurocardiac disease, at least in some cases.

These and other studies provide accumulating evidence that in some who experience SUDEP, mutated genes coexpressed in the heart and the brain lead to epilepsy and arrhythmia. In others, however, there may be coincidental predisposition to cardiac death (whether monogenic or polygenic), which may be more likely to manifest in the context of uncontrolled convulsions. The Australian studies suggest these categories represent an important minority of SUDEP cases.

In addition to prevention of convulsions and assistance at the time of a seizure, we now have another potential avenue for SUDEP prevention, one as yet unexplored. Genes do not recognize the arbitrary divisions of specialization today. Neurologists must consider the heart and cardiologists the brain. Family studies, with a good yield in sudden cardiac death, are needed in SUDEP. We will need prolonged EEG recordings of selected cases of LQTS to clarify with more certainty when seizures in LQTS are due to epilepsy or epilepsy mimics. This chapter on genetic predisposition to SUDEP is not yet complete, but this important study by Auerbach and colleagues adds new insight to knowledge.

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