

Seizures and Sudden Death Beyond SUDEP

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Many physicians and researchers are familiar with the tragic phenomenon known as sudden infant death syndrome (SIDS), the leading cause of postneonatal mortality in high-resource countries. A less familiar category of unexplained deaths is the problem of sudden unexplained death in childhood (SUDC), a more rare and unusual presentation of sudden death in children who are no longer infants and whose reasons for death defy explanation. A substantial body of research in SUDC now supports the possibility of an overlap with epilepsy and associated sudden death in that context (SUDEP). Stemming from the first contemporary reports of SUDC, we have learned that a disproportionate number of these children have personal and/or family histories of febrile seizures,¹ in many cases, inherited in an autosomal dominant manner.² Their febrile seizures can be associated with abnormalities in their temporal lobes,^{3,4} including bilamination of the dentate gyrus and other findings conventionally associated with temporal lobe epilepsy, implicating potential epilepsy-related mechanisms.⁵ Further evaluation of this emerging epilepsy-related phenotype has led to the identification of genetic variants in *SCN1A* and other epilepsy-associated genes,^{6,7} moving SUDC away from being considered an unexplained phenomenon to one where the working hypothesis includes a role for genetic predisposition and epilepsy-like mechanisms in the deaths, even without an established history of epilepsy. Nonetheless, because the terminal events of these seemingly healthy children are unexpected and unobserved, the clinical manifestations of whatever underlying vulnerabilities exist—generally discovered posthumously—remain a matter of speculation.

In this issue of *Neurology*®, Gould et al.⁸ contribute further evidence that seizures likely play a role in at least some cases of sudden death in children. In a series of important observations that consolidate work in this area, the authors' "Video Analyses of Sudden Unexplained Deaths in Toddlers" presents terminal videos from a series of 4 boys and 3 girls, aged 13–27 months, whose deaths were classified as SUDC. All but one of the videos showed persuasive evidence of a convulsive event in the minutes before the child's death. All were normally developing children with unremarkable medical histories. Six of the children were found prone, 1 turned to the side. One child had a history of febrile seizures and a family history of febrile seizures and epilepsy, and half of the cases with neuropathologic assessments (3 of 6) had abnormalities in their dentate gyrus.

It would be hard to overestimate the impact of the MORTEMUS study of SUDEP deaths in monitoring units,⁹ which encouraged researchers to expand their attention beyond the moment of death to the immediate antemortem period. With the same rationale, Gould et al. evaluated evidence for apparently convulsive activity preceding deaths from SUDC. While the study lacks the electrophysiologic monitoring that would formally establish the presence of electroclinical seizures, the team largely found consensus that there is convulsive activity in their review of the videotapes. The authors make the point that the children included in this series are representative of all the deceased children in their program's larger cohort. Given the small sample size and the possibility of ascertainment bias, it is too early to know how generalizable their findings are.

This report raises many important questions. What are the implications for SIDS, where abnormalities of the dentate gyrus¹⁰ and similar epilepsy-associated genetic findings have also

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been found?⁷ How does this affect our understanding of the significance of the prone position in SIDS because SIDS, SUDC, and SUDEP deaths are primarily discovered in the prone position? Should these emerging data affect our understanding of, and counseling for, febrile seizures in children?

Moreover, acknowledging our incomplete understanding of the genetic mechanisms underlying SIDS and SUDC, it seems necessary to contemplate the role genetics may have played for the toddlers described by the authors. While the specifics of the genetic analyses of the 7 children are not presented, the lack of pathogenic variants in genes such as *SCN1A* or *DEPDC5*, or any pathogenic or likely pathogenic variants identified by analysis of whole-exome sequencing data, does not preclude a genetic contribution. Indeed, it raises questions about whether these children may have had noncoding variants in known genes, variants in additional genes, or genetic processes not yet considered because the application of genetics to the problem of early child death in previously well children is so nascent.

While the article affords consideration to cardiac etiologies, it is fair to say that this report heralds new avenues for investigation and reshapes the significance of neurologic study into unexplained deaths in infants and children. Seizures in infants and children can be difficult to diagnose, and the risk of SUDEP in children with epilepsy is an ongoing debate, made more complex when considering potential genetic and neuropathologic overlap between SIDS, SUDC, and SUDEP. As this study shows, there is strength in understanding a problem in a broader context, just as there is strength in the steady, disciplined scientific study that makes new advances possible. Gould et al. took on a key question—do children dying with SUDC have seizure activity before death? This early report suggests we look more closely. It is our hope that such work

continues at larger scale with renewed focus and our greater hope that such deaths will ultimately become preventable.

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