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Through the Lens: Insights Into Sudden Death

Video Analyses of Sudden Unexplained Deaths in Toddlers

Gould L, Reid CA, Rodriguez AJ, Devinsky O; for SUDC Video Working Group. *Neurology*. 2024;102(3):e208038. doi:10.1212/WNL.0000000000208038. PMID: 38175965

Background and objectives: More than 2,900 US children aged younger than 4 years die from unknown causes each year, accounting for more than 219,000 life years lost annually. They are mostly sleep-related and unwitnessed with unremarkable autopsies, limiting our understanding of death mechanisms. We sought to understand potential mechanisms of death by evaluating videos of sudden deaths in toddlers. Methods: In our registry of 301 sudden unexplained child deaths, a series of 7 consecutively enrolled cases with home video recordings of the child's last sleep period were independently assessed by 8 physicians for video quality, movement, and sound. Results: Four boys and 3 girls (13-27 months at death) with terminal videos shared similar demographic features to the 293 other registry cases without video recordings. Five video recordings were continuous and 2 were triggered by sound or motion; 2 lacked audio. All continuous recordings included a terminal convulsive event lasting 8-50 seconds; 4 children survived for >2.5 minutes postconvulsion. Among discontinuous videos, time lapses limited review; 1 suggested a convulsive event. Six were prone with face down, and 1 had autopsy evidence of airway obstruction. Primary cardiac arrhythmias were not supported; all 7 children had normal cardiac pathology and whole-exome sequencing identified no known cardiac disease variants. Discussion: Audio-visual recordings in 7 toddlers with unexplained sudden deaths strongly implicate that deaths were related to convulsive seizures, suggesting that many unexplained sleep-related deaths may result from seizures.

Exome Analysis Focusing on Epilepsy-Related Genes in Children and Adults With Sudden Unexplained Death

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Purpose: Genetic studies in sudden infant death syndrome (SIDS) and sudden unexplained death (SUD) cohorts have indicated that cardiovascular diseases might have contributed to sudden unexpected death in 20% to 35% of autopsy-negative cases. Sudden unexpected death can also occur in people with epilepsy, termed as sudden unexpected death in epilepsy (SUDEP). The pathophysiological mechanisms of SUDEP are not well understood, but are likely multifactorial, including seizure-induced hypoventilation and arrhythmias as well as genetic risk factors. The sudden death of some of the SIDS/SUD victims might also be explained by genetic epilepsy, therefore this study aimed to expand the post-mortem genetic analysis of SIDS/SUD cases to epilepsy-related genes. Methods: Existing whole-exome sequencing data from our 155 SIDS and 45 SUD cases were analyzed, with a focus on 365 epilepsy-related genes. Nine of the SUD victims had a known medical history of epilepsy, seizures or other underlying neurological conditions and were therefore classified as SUDEP cases. Results: In our SIDS and SUD cohorts, we found epilepsy-related pathogenic/likely pathogenic variants in the genes OPA1, RAI1, SCN3A, SCN5A and TSC2. Conclusion: Post-mortem analysis of epilepsy-related genes identified potentially disease-causing variants that might have contributed to the sudden death events in our SIDS/SUD cases. However, the interpretation of identified variants remains challenging and often changes over time as more data is gathered. Overall, this study contributes insight in potentially pathophysiological epilepsy-related mechanisms in SIDS, SUD and SUDEP victims and underlines the importance of sensible counselling on the risk and preventive measures in genetic epilepsy.

Commentary

Sudden unexpected death in epilepsy (SUDEP) is a rare but devastating complication, estimated to occur in approximately 1 per 1000 person-years in children and adults with epilepsy.[1] While the exact mechanisms are unknown, evidence suggests that a generalized seizure results in failure of central mechanisms of cardiorespiratory function resulting in apnea, bradyarrhythmia, and eventual circulatory collapse.[2,3] While SUDEP is at the forefront of our minds when it comes to epilepsy, there are other syndromes associated with sudden death; sudden infant death syndrome (SIDS), sudden unexplained death in childhood (SUDC), and sudden unexplained death (SUD). The dearth of research into these entities leaves many unanswered questions; however, from studies into SIDS and SUDC we know that these events are most likely to occur from sleep and more commonly happen to infants, especially with prone positioning. There is increased incidence in winter months, in males, and in those with recent or intercurrent illness. There may be a febrile seizure history.[4] Given commonalities in patients with sudden unexplained death, are there other features that link these sudden death syndromes?

In their study utilizing the Sudden Unexplained Death in Childhood Registry, Gould and colleagues looked at terminal video footage from monitoring devices in 8 patients within their cohort of 301 patients.[5] Seven cases with terminal video were included (one excluded due to poor video quality), with ages ranging from 13 to 27 months, including 4 males, with prior normal development and benign past medical histories. All deaths were sleep-related and all but one child was discovered with their face prone in bedding. Four had symptoms such as cough, fever, cold symptoms, and teething in the 72 hours prior to death with postmortem analysis finding mild signs of infection in 6 which were not felt to be causative. Six cases were ultimately ruled "Unexplained Sudden Death" with the remaining case considered asphyxia from airway obstruction in the setting of viral/bacterial infection. Whole exome sequencing was unrevealing.

The authors also examined the remaining cohort, stratified by age less than or greater than 60 months ($n = 248$ vs $n = 53$, respectively). It was notable that in both groups, most children achieved normal milestones and only a small number had a history of prematurity. Statistically significantly ($P < .001$), in the $\leq$60 months group, 29.4% had a history of febrile seizures and 20.6% had a first degree relative with a history of febrile seizures. Other strongly significant findings in the $\leq$60 months group included cold symptoms and/or fever within 48 hours of death (46.8%), sleep-related event (93.5%), body prone positioning (83.1%), and death being unwitnessed (94.4%).

The key finding from this study was that convulsive events preceded death in all cases. In 5 records with continuous video, a convulsive event was seen before death and audio in 4 out of 5 records with sound identified agonal, labored, or abnormal deep breathing. In the 2 motion-triggered videos, the potential semiology was less clear compared to continuous recordings. However, 5 children were felt to have convulsive semiology, one hypermotor semiology, and the final child had indeterminant movements. The authors included brief descriptive timelines of convulsive activity, vocalizations, and respiratory activity post seizure until death, highlighting the abnormal breathing patterns that followed the convulsive events until death.

The findings in this study, while sobering, are consistent with those previously reported in the MORTEMUS trial of monitored SUDEP, specifically the cardiorespiratory depression and post-ictal breathing patterns.[2] While a relationship between SIDS, SUDC, and SUDEP have been speculated, this study strongly suggests that connection may go beyond a shared final pathway of cardiorespiratory depression and suggests a shared inciting mechanism, that is, seizure-related central cardiorespiratory depression. This does not imply that a seizure precedes every case of sudden death. Certainly, it has been reported that SUDEP can occur interictally in persons with epilepsy.[6]

Further exploring the relationship between SUD and SUDEP, prior work has identified pathogenic variants expressed in both brain and heart to investigate if a genetic susceptibility to seizure-induced cardioarrhythmia may be a mechanism for unexplained death.[7,8] In their retrospective whole-exome analysis (WES) of subjects in a Swiss SIDS and SUD database, Buerki et al looked at previously performed WES, filtering for 365 genes associated with epilepsy.[9] The authors evaluated 155 SIDS and 45 SUD cases, for pathogenic and likely pathogenic heterozygous variants. On 2-year reclassification, 8 pathogenic variants in autosomal recessive disorders and 3 likely pathogenic variants with autosomal dominant inheritance (*OPA1*, *RAI1*, and *TSC2*) were found in the SIDS group. In the SUD group, a pathogenic variant in *SCN5A* and a likely pathogenic variant in *SCN3A* were found, with remaining 4 variants associated with autosomal recessive disorders. Five SUD cases had epilepsy and 4 were felt to be consistent with SUDEP. For these cases, variants included *SCN5A*, *BTD*, and *RMND1* while the fourth case had a history of isodicentric chromosome 15. The authors later clarify in the discussion that of the 45 total SUD cases, 9 were classified as SUDEP. There was not additional history provided for cases, such as febrile seizure history or family history of epilepsy.

These results should be taken with a grain of salt. The unanswered question is whether a pathogenic or likely pathogenic variant in an epilepsy susceptibility gene increases future risk of sudden unexpected death. One SIDS case had a variant in *TSC2*, associated with Tuberous Sclerosis Complex, and another a pathogenic variant in *RAI1*, associated with Smith-Magenis syndrome, both of which can have varying clinical severity and age of presentation, but there was no phenotyping presented for these cases. Given the variable penetrance with both syndromes, this limitation makes it challenging to draw any conclusions from the identification of these variants. The authors performed reanalysis and reclassification of the identified variants after 2 years, which highlights how variants can be reclassified as benign or variants of uncertain significance

based on subsequently reported phenotypes, in-silico analyses, and functional studies. One of the major overall limitations of this paper was the lack of additional clinical detail and absent phenotypes. Additional information was available for those patients who experienced SUDEP, but the promise of the article was uncovering epilepsy susceptibility genes in those with SIDS and SUD, yet the focus ultimately shifted to SUDEP without making the necessary connections and limiting the generalizability of the findings. This study highlights that there could be a genetic susceptibility in sudden death syndromes, which is not a new finding.[7,8]

The findings of both studies could only be identified retrospectively but are still important in further understanding these entities. There are limitations to terminal video monitoring studies as routine use of audio-video monitoring is variable in children and it would be challenging to advocate for universal use of this technology to record terminal events. Similarly, routine epilepsy genetic screening in asymptomatic individuals, particularly minors without the ability to consent, would be hard to justify.

These studies offer clues into potential contributing factors associated with sudden unexplained death in children and adults. Future work needs to be done on these devastating conditions to identify modifiable risk factors so we can prevent SIDS, SUDC, and SUDEP. Maybe one way forward is to truly start investigating sudden death as a spectrum rather than focusing on one individual population, that is, infants or persons with epilepsy. Overall, these articles highlight that in some individuals there is likely a link between seizures and sudden death, whether it is a shared pathophysiology between the sudden death syndromes, certain genetic susceptibilities, environmental and biologic factors, or in some cases, a first-time, terminal seizure.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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