H35 Sudden Cardiac Death and Epilepsy-Related Gene Mutations in Sudden Unexpected Death in Epilepsy (SUDEP)

Andrew S. Williams, MD, Ontario Forensic Pathology Service, Forensic Services and Coroner's Complex, 25 Morton Shulman Avenue, Toronto, ON M3M 0B1, CANADA; Anne E. Keller, MPH, The Hospital for Sick Children, Division of Neurology, 555 University Avenue, Toronto, ON M5G 1X8, CANADA; Robyn Whitney, MD, The Hospital for Sick Children, Division of Neurology, 555 University Avenue, Toronto, ON M5G 1X8, CANADA; Kris Cunningham, MD, Ontario Forensic Pathology Service, 25 Morton Shulman Drive, Toronto, ON M3M0B1, CANADA; Michael S. Pollanen, MD, PhD, Ontario Forensic Pathology Service, 25 Morton Shulman Avenue, Toronto, ON M3M 0B1, CANADA; and Elizabeth J. Donner, MD, MSc, The Hospital for Sick Children, Division of Neurology, 555 University Avenue, Toronto, ON M5G 1X8, CANADA*

After attending this presentation, attendees will be able to define SUDEP, understand the application of the definition to individual cases, describe contemporary theories on the mechanism of death in SUDEP, and list several "neurocardiac" genes currently under investigation as biomarkers of SUDEP risk.

This presentation will impact the forensic science community by updating attendees on the theoretical mechanisms of death in SUDEP and how these relate to potential individual genetic differences in "neurocardiac" genes and by reinforcing the definition of SUDEP for uniform cause-of-death certification in these cases.

Background: SUDEP is a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in an individual with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a cause of death.[1] This definition does not predicate that the epilepsy be primary or idiopathic epilepsy. SUDEP is a leading cause of epilepsy-related premature mortality, with an estimated incidence of 1.22/1,000 persons with epilepsy, accounting for more deaths on an annual basis than Sudden Infant Death Syndrome (SIDS).[2] The precise mechanism by which epilepsy results in death remains unknown. Several theories have been proposed, including cardiac arrhythmia, respiratory failure, and "electrocerebral shutdown".[3]

A major difficulty in the clinical treatment of epilepsy is that it is not understood why some individuals die of SUDEP while other patients with epilepsy of a similar "severity" survive.[3,4] One possibility is that those who die of SUDEP have an underlying genetic mutation in a gene related to ion transportation or cardiac function that predisposes them to sudden death.[5] The current work was undertaken to assess the proportion of cases of SUDEP that demonstrate genetic changes in genes associated with sudden cardiac death and/or epilepsy.

Methods: Cases were selected from autopsies performed between January 1, 2014, and December 31, 2016, through the Ontario Forensic Pathology Service. Genetic testing was performed on 36 cases that had been signed out by the pathologist with the cause of death given as SUDEP and that had a sample suitable for genetic testing. Analysis was performed by GeneDx®. Each case was assessed by the Sudden Cardiac Arrest Panel ((SCAP) 120 genes) and Comprehensive Epilepsy Panel ((CEP) 87 genes).

Results: The 36 cases were comprised of 21 males and 15 females, with ages ranging from 3 years to 60 years. Variants of Uncertain Significance (VUS) in SCAP panel genes were detected in 20 cases (proportion with SCAP VUS: 55%) and involved 20 genes. VUS in the following genes was detected in multiple individuals (*n*): *SCN10A* (5), *RYR2* (4), *SCN5A* (2), *LMNA* (2), *TTN* (2). VUS in CEP panel genes were detected in 20 cases (proportion with CEP VUS: 55%) and involved 26 genes. VUS in the following genes was detected in multiple individuals (*n*): *PIGO* (2), *PNKP* (2). Ten cases were called negative on both the SCAP panel and CEP panel (proportion with SCAP or CEP VUS: 72%). No known pathogenic variants were detected. Further in-depth analyses of the VUS are ongoing.

Conclusions: This preliminary interrogation of genes associated with sudden cardiac death and/or epilepsy in a cohort of patients dying of SUDEP reveals a high prevalence of variants currently classified as VUS. Several genes displayed multiple variants across several individuals, which is an intriguing result, and further analyses of the specific variants are ongoing. Forensic pathologists should be aware that the leading mechanistic theories of death in SUDEP involve cardiac arrhythmia, respiratory failure, and electrocerebral shutdown. Genetic variations may account for why some patients with epilepsy die of SUDEP while others survive.

Reference(s):

1. Nashef L., So E.L., Ryvlin P., Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia.* 2012:53(2):227-233.
2. Thurman D.J., Hesdorffer D.C., French J.A. Sudden unexpected death in epilepsy: Assessing the public health burden. *Epilepsia.* 2014:55(10):1479-1485.
3. Dlouhy B.J., Gehlbach B.K., Richerson G.B. Sudden unexpected death in epilepsy: Basic mechanisms and clinical implications for prevention. *J Neurol Neurosurg Psychiatry.* 2016:87:402-413.
4. Glasscock E. Genomic biomarkers of SUDEP in brain and heart. *Epilepsy Behav.*2014:Sep(38):172-179.
5. Goldman A.M., Behr E.R., Semsarian C., Bagnall R.D., Sisodiya S., Cooper P.N. Sudden unexpected death in epilepsy genetics: Molecular diagnostics and prevention. *Epilepsia.* 2016:Jan(57-Suppl 1):17-25.

Epilepsy, SUDEP, Sudden Death

*Presenting Author