The SUDC Foundation
549 Pompton Avenue, Suite 197
Cedar Grove, NJ 07009

www.sudc.org
800.620.SUDC (7832)
Direct in U.S. 973.239.4849

MEDICAL AND BEREAVEMENT INFORMATION TO HELP CLINICIANS WHEN CARING FOR FAMILIES

Families who have experienced the sudden unexplained death of their baby or child often ask, “Should I have my other children tested?” This important question may be followed by the response of “Test them for what?” At this time, we do not know how to predict or prevent SIDS/SUDC. However, we do know that some rare inheritable disorders can cause sudden unexpected death. We also know that death investigations, as well as state mandated newborn screenings, vary across the U.S. Therefore, it is difficult to recommend one specific set of tests for all families who have suffered an unexplained childhood death.

Research in the area of inherited disorders continues, and with the completion of the human genome project, new information is being attained. The ability to diagnose and treat individuals with these conditions continues to save lives and maximize the health of those affected. Without diagnosis and treatment, disorders such as Long QT Syndrome and various metabolic disorders would continue to be the cause of sudden unexpected deaths in children and some adults. Following optimal pediatric care guidelines including: attending well child visits, maintaining current vaccinations, following safe sleep guidelines in infancy (such as those of the AAP) and obtaining appropriate health care when clinically indicated are recommended.

In addition, the following information is to be considered with families who have suffered the sudden loss of a child where the cause of death is unknown or unclear. The information is general and does NOT provide specific recommendations for any particular family, but provides a basis for discussions with families in need in order to determine appropriate screening tests, ensure accurate diagnoses and help provide some peace of mind for surviving family members. Collaboration of specially trained medical professionals is necessary to provide optimal care for the bereaved family. Discussing these initially with your doctor, pathologist who performed the autopsy, your child’s pediatrician and additional appropriate medical specialists should be helpful in coordinating an appropriate specific testing plan for present family members, as well as for future pregnancies and subsequently born

children. Your doctor or pediatrician may recommend other tests, in addition to the following, based on your specific family history and the circumstances and information known regarding the child who died.

Evaluating Inborn Errors of Metabolism

Some questions to consider:

- What was the extent and result of the state mandated newborn screening test?
- performed after the birth of the child who died? (Resource: www.savebabies.org)
- Is the newborn card available now for retrieval?
- Did the child, who died, have vomiting, decrease appetite, lethargy, febrile illness etc. in the days preceding their death which raise the concern of metabolic disease?
- Did the pathologist discover autopsy findings, medical history findings or terminal history findings that raise the concern for metabolic disease?
- What was the extent and result of port mortem metabolic studies performed on the child who died?

Evaluating Siblings:

- During the PRENATAL period:
  - Get regular and early prenatal care.
  - Special consideration should be given to the possible occurrence of maternal complications: Acute Fatty Liver of Pregnancy (AFLP); Hemolysis, Elevated Liver (enzymes), Low Platelets Syndrome (HELLP); Pre-Eclampsia, and others
- For the Asymptomatic SUDC/SIDS/SUID Sibling NEWBORN:
  - Blood: Expanded newborn screening by MS/MS (blood spots)—If this is not mandated in your state, bloodspot cards can be requested ahead of time from private labs. (Information on some available labs can be obtained from the SUDC Foundation)
  - Urine: Organic Acids
  - Consider repeating above at time of first illness
- For the Symptomatic SUDC/SIDS/SUID Sibling NEWBORN:
  - If the newborn is not well—Seek emergency medical attention immediately, and include specialists in metabolic disease.
  - Start evaluation with investigations that include:
    - Blood Gases, Glucose, Electrolytes, Lactate, Pyruvate, Ammonia
    - Urine-Organic Acids
- For Older Siblings of SUDC/SIDS/SUID:
  - PLASMA Acylcarnitines and Urine Organic Acids

- If expanded newborn screening, plasma acylcarnitines and organic acids are all negative, the pursuit of additional targeted tests should be considered on a case-by-case basis, also determined by the outcome of the postmortem investigation in the child who died suddenly.
- Consider repeating above during time of illness

References

- Rinaldo P, Matern D, Bennett MJ. Fatty acid oxidation disorders. Ann Rev Physiol 64:16.1-26, 2002.
- Bennett MJ, Rinaldo P. The Metabolic Autopsy comes of Age. Clinical Chemistry 47; 1145-6, 2001
- Tortorelli S, Hahn SH, Cowan TM, Brewster TG, Rinaldo P, Matern D. The urinary excretion of glutarylcarnitine is an informative tool in biochemical diagnosis of glutaric acidemia type 1. Molecular Genetics and Metabolism 84:137-143, 2005
- Mayo Medical Laboratories Communiqué on postmortem testing

Evaluating Cardiac Channelopathies

In addition to discussion of PMH of child who died, their post mortem findings and the family's medical history, consider these specific questions to consider and discuss:

- Is there Family History of Sudden Death in those under 40 years of age?
- Is there Family History of Unexplained Syncope, Sleep disorders, ALTE or Seizures?
- Is there history of Syncope, Sleep disorders, ALTE, Seizures in child who died?

Although heart muscle and congenital abnormalities, tumors and infection can be evaluated during the standard autopsy procedures, some cardiac abnormalities require a molecular autopsy and/or careful examination of surviving family members for full evaluation.

Therefore, in 2011, the HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for Channelopathies and Cardiomyopathies published in Heart Rhythm, Vol 8, No 8, August 2011 provided recommendations on the
"STATE OF POST-MORTEM GENETIC TESTING IN SUDDEN UNEXPECTED DEATH CASES (SUD/SIDS)"

The Expert Consensus Recommendations concluded:

1. For all SUDS and SIDS cases, collection of a tissue sample is recommended (5
2. –10 mL whole blood in EDTA tube, blood spot card, or a frozen sample of heart, liver, or spleen) for subsequent DNA analysis/genetic testing. In the setting of autopsy-negative SUDS, comprehensive or targeted (RYR2, KCNQ1, KCNH2, and SCN5A) ion channel genetic testing may be considered in an

attempt to establish probable cause and manner of death and to facilitate the identification of potentially at-risk relatives and is recommended if circumstantial evidence points toward a clinical diagnosis of LQTS or CPVT specifically (such as emotional stress, acoustic trigger, drowning as the trigger of death).

3. Mutation-specific genetic testing is recommended for family members and other appropriate relatives following the identification of a SUDS-causative mutation in the decedent.
   Discussions regarding genetic testing of Cardiac Channelopathies among families and their Physicians need to consider what genetic samples are available for testing from the child who died and consider the testing options listed below:

<u>Screening the Child who Died</u>

Post Mortem Evaluation of Cardiac Channelopathies in the child who died: Options through Research and Commercial Testing

- Commercial, clinical testing for Cardiac Channelopathies through private labs, such as:
  - FAMILION (www.familion.com),
    - Length of time from testing to results: about 4-6 weeks,
    - Participation requires blood in EDTA, and the post mortem screening panel~costs $2500.
    - Postmortem genetic testing is so far unlikely to be paid for by insurance.
    - It tests for 5 of the known Long QT Syndrome genes. Participation requires blood in EDTA, or autopsy tissue specimens.
- Gene DX
  - Postmortem genetic testing is so far unlikely to be paid for by insurance.
- Genetic testing via research
- Mayo Clinic's Sudden Death Genomics Laboratory
  - IRB-approved, free, and consent of appropriate next of kin is required. Here, the focus is on discovery and the research subject's specific "service" is a hoped for result with successful elucidation of novel causes for sudden unexplained death.
  - Length of time from testing to results: SLOW! Usually more than one year. In general, contact with the medical examiners and families only occur in the event that the research testing identifies a probable genetic cause.
    Participation: Requires DNA from deceased that is adequate for testing (i.e., frozen tissue that is DNA rich, blood in EDTA, blood spot cards). In general, formalin fixed tissue and paraffin-embedded tissue will NOT permit a successful molecular autopsy.
  - Contact: Long QT Syndrome Clinic # (507) 284-0101.

Any positive genetic finding requires detailed analysis to determine of the identified mutation is truly disease-causing or a benign variant. This can be supported by clinical and genetic evaluation of surviving family members.

Screening Family Members

Evaluation of Cardiac Channelopathies in Family Members of cases of sudden unexplained death or sudden cardiac death.

Since channelopathies can be inherited, other biological relatives may be at risk. Therefore, evaluation of family members for long QT Syndrome and other inherited arrhythmia conditions is appropriate to both confirm a family diagnosis and assess the risk in the living family members following an unexplained death or a sudden cardiac death. Clinical evaluation of family members following a sudden death may identify other affected members and hence provide a diagnosis in up to 40% of families (Ref Tan), and may be supported by any genetic findings.

First Degree Relatives (Parents and Siblings of the person who has died) should speak to their Primary Physician to obtain a referral to a Cardiologist (with expertise in electrophysiology and special training to evaluate genetic cardiac disorders) to perform:

1. A VERY careful and detailed medical history of the decedent with review of the autopsy report and sometimes the autopsy tissue itself by a specialist cardiac pathologist.
2. A VERY careful and thorough review of the family history with pedigree analysis on both sides searching for the relevant history or events on either side of the family. Current research has found a greater incidence of channelopathies diagnosed postmortem with the greater age of the child. Therefore, in older children where the autopsy fails to demonstrate any structural abnormalities, a clinical screen should be performed in surviving family members to assess for the possibility of inherited heart rhythm syndromes.
    - Clinical screening tests would include: a. ECG/EKG, b. Holter, and c. Exercise Stress Test (Exercise stress test recommendation is based on the findings and recommendations of the 3rd reference below, due to CPVT escaping detection by a resting electrocardiogram).
    - Any additional provocative tests (i.e epinephrine QT stress test, procainamide stress test, or isoproterenol stress test, or diagnostic EP study) would be based upon the clinical impression, family history, etc.
    - If directed by results of such investigations, molecular genetic testing for a "cardiac channelopathy" like long QT syndrome should be pursued.
1. Pursue channelopathy panel screening on the decedent.

Locating a Specialist for Screenings:

Links to some comprehensive clinics in cardiogenetics can found via The SUDC Foundation's website.

Additional online resources to find a specialist in your area include:

- The Pediatric and Congenital Electrophysisology Society
- The SADS Foundation

If you are having trouble locating a specialist, please contact the SUDC Foundation (toll free in the U.S) at 800-620-SUDC (7832) or direct dial at 973-239-4849.

What is Long QT Syndrome (LQTS)?

By Michael J. Ackerman, MD, PhD

Long QT Syndrome (LQTS) is a disorder of the electrical system of the lower chambers of the heart (ventricles). The mechanical or pumping function of the heart is normal. However, the recharging (repolarization) system of the heart is either slow, taking longer than normal to recharge, or inefficient (disorganized). LQTS can be divided into two broad categories: congenital and acquired. In acquired LQTS, the electrical recharging abnormality is secondary to medications, abnormalities in electrolytes, or other illnesses (like anorexia nervosa for example) that prolong the QT interval. In contrast, congenital LQTS is known as a primary cardiac ion channel disease due to mutations in the genes encoding the proteins (ion channels) responsible for this electrical recharging process. It is estimated that 1 in 3000 persons may have congenital LQTS. The symptoms of LQTS vary tremendously from NO symptoms ever (about 40-50%) to fainting/seizure spells (40-50%) in the setting of exercise like swimming, auditory startles (alarm clocks, phone, doorbells) to sudden death (5–10%). Since the heart's structure and mechanical performance is normal in LQTS, there are no clues found at autopsy. In fact, LQTS should be considered strongly for any sudden unexplained death accompanied by a normal autopsy. An estimated 5 – 15% of sudden infant death syndrome may be caused by LQTS-causing genetic defects. In a postmortem investigation of SUD victims where the average age was 14 years, 20% of the decedents were found to have mutations in LQTS genes. Based upon this data, it is strongly recommended that a careful family history be obtained and screening electrocardiograms of first degree relatives (parents, children, siblings) be considered in the setting of a sudden unexplained and autopsy negative death. Postmortem genetic testing of DNA from the decedent should become the standard of care in the evaluation of SUD but this is hindered presently by the cost of genetic testing and the apparent reluctance of health insurance companies to reimburse for such diagnostic testing despite the potential lifesaving, not to mention cost saving, benefit for the loved ones left behind.

References:

- Ackerman et al. HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for Channelopathies and Cardiomyopathies. Heart Rhythm, Vol 8, No 8, August 2011
- Ackerman MJ, Tester DJ, Driscoll, DJ. Molecular autopsy of sudden unexplained death in the young. The American Journal of Forensic Medicine and Pathology. 2001; 22(2): 105-111.
- Ackerman MJ, Khosiseth A, Tester DJ, Hejlik J, Shen WK, Porter CJ. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. Mayo Clinic Proceedings. 2002;77:413-421.
- Tester DJ, Spoon DS, Valdivia HH, Makielski JC, Ackerman MJ. Targeted Mutational Analysis of RyR2-Encoded Cardiac Ryanodine Receptor in Sudden Unexplained Death: A Molecular Autopsy of 49 Medical Examiner/Coroner Cases. Mayo Clinical Proceedings, 2004, 79 (11): 1380-1384 www.mayo.edu/proceeding
- Tan H, Hofman N, Van Langen IM, Van Der Wall AC, Wilde AAM. Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. Circulation 2005;112: 207-213.

Evaluating Seizures in Siblings of SUDC

Tips for Meeting the Emotional Needs of Bereaved Parents of a Sudden Unexpected Death

Evaluating Seizures in Siblings of SUDC

Families entering the SUDC Research Project to date are reporting a higher than expected incidence of seizures, especially febrile seizures, in the child who died and sometimes family members as well. Medical literature over the last several decades reports on the benign nature of simple febrile seizures. At this time, we recommend a neurological consultation for all SUDC siblings who have a history of seizures (febrile or without fever) or any other neurological concern (e.g., developmental delay) with a pediatric neurologist.

The articles below may provide some information and guidance to families and physicians. At this time, since the association between SUDC and febrile seizures is still being investigated, we cannot make any general recommendations about the specific evaluation and treatment of febrile seizures in siblings of children who have died of SUDC.

If, at any time, contact with The SUDC Foundation for more information and/or direct contact with our researchers or physicians would be helpful in evaluating these children, please call Laura Crandall toll free in the U.S. at 800-620-SUDC (7832) or direct dial 973-239-4849.

References

- Ingrid A. Holm MD, MPH, Annapurna Poduri MD, MPH, Laura Crandall PT, MA, Elisabeth Haas MPH, Marjorie R. Grafe MD, PhD, Hannah C. Kinney MD, Henry F. Krous MD, Inheritance of Febrile Seizures in Sudden Unexplained Death in Toddlers. Pediatric Neurology 46 (2012) 235e239
- Mazumdar, M Febrile Seizures and Risk of Death (editorial) Lancet. 2008; Vol 372:429-430.
- Kinney HC, Armstrong DL, Chadwick AE, et al. Sudden Death in Toddlers Associated with Developmental Abnormalities of the Hippocampus: a report of five cases. Pediatr Dev Pathol. 2007;10(3):208-223.
- Krous HF, Chadwick AE, Crandall L, Nadeau-Manning. Sudden Unexpected Death In Childhood: A Report of the 50 Cases. Pediatrci Dev Pathol. 2005 July 14

Tips for Meeting the Emotional Needs of Bereaved Parents of a Sudden Unexpected Death

Meeting and working with bereaved families can be unusual for clinicians who are not often exposed to individuals in acute grief and therefore they may feel unprepared. In addition, specific training in this area may not have been received in their formal training. Families can relate to this. They were also unprepared to deal with the death and grief of their child, and therefore can be very understanding of a clinician feeling like they are in uncharted waters as well. Compassion and patience, when working with bereaved families, is key for a successful partnership.

Grief is a natural process of emotions that occurs when someone dies. Grief integrates into normal routines at variable timeframes for each person. Complicated grief can occur when initial grief emotions continue and significantly impact functioning over the long term.

Trauma can also be a component of grief when someone they love dies suddenly and unexpectedly, especially a child. This can leave survivors to feel helpless, vulnerable and often powerless. Trauma symptoms typically last from a few days to a few months, gradually fading as the emotional trauma is processed. Acceptance, processing the event and time are a part of the recovery process.

Emotional and Psychological Symptoms of Trauma may include:

- Shock, denial, or disbelief
- Anger, irritability, mood swings
- Guilt, shame, self-blame
- Feeling sad or hopeless
- Confusion, difficulty concentrating
- Anxiety and fear
- Withdrawing from others
- Feeling disconnected or numb

Physical Symptoms of Trauma may include:

- Insomnia or nightmares
- Being startled easily
- Racing heartbeat
- Aches and pains
- Fatigue
- Difficult concentrating
- Edginess and agitation
- Muscle tension

Therapeutic Approaches

Trauma disrupts the body's natural equilibrium, putting one in a state of hyper arousal and fear. The purpose of specific therapeutic approaches therapies is to address this imbalance and reestablish a sense of safety.

- Somatic experiencing takes advantage of the body's unique ability to heal itself. The focus of therapy is on bodily sensations, rather than thoughts and memories about the traumatic event. By concentrating on what's happening in the body, natural survival instincts take over, safely releasing this pent-up energy through shaking, crying, and other forms of physical release.
- EMDR (Eye Movement Desensitization and Reprocessing) incorporates elements of cognitive-behavioral therapy with eye movements or other forms of rhythmic, left-right stimulation. These back-and-forth eye movements are thought to work by "unfreezing" traumatic memories, allowing resolution.
- Cognitive-behavioral therapy processes and evaluates thoughts and feelings that surround a trauma. While cognitive behavioral therapy doesn't treat the physiological effects of trauma, it can be helpful when used in addition to a body based therapy such as somatic experiencing or EMDR.

Working through trauma can be scary, painful, and potentially re-traumatizing. Because of the risk of re-traumatization, this healing work is best done with the help of an experienced trauma specialist.

When Communicating with Families Consider:

The following tips and resources may additionally assist the professional in caring for a bereaved family, and may also help the bereaved family communicate their needs:

- No two individuals grieve alike. Although there are some gender stereotypes and common cultural traditions in coping with death, remember that no two individuals grieve alike. Grief is unique to that individual.
- Grief is exhausting–recognize that the capacity to participate in medical discussions may be limited and be sure to provide instructions in writing. The ability to multitask, or focus on any task for a prolonged period is difficult in acute grief.
- Be patient and understanding. Healing from emotional or psychological trauma takes time. Be patient with the pace of recovery and remember that everyone's response to trauma is different. Don't judge one's reaction against your own response or anyone else's.
- Acknowledge the child's death by providing your sympathies to the family.
- Demonstrate that it is permissible to discuss their child who died and to express their emotions-including crying.

- Use the name of the child who died (do not refer to them as "the child who died"). Know their birth date and date of death, and recognize that meeting them close to a special date might be additionally stressful for them.
- Be honest and clear on what information is known and not known about the death of the child. Be clear about what is speculative and what is medical fact.
- Assess their psychosocial support and coping skills and offer mental health support referrals as appropriate. Be alert to signs and symptoms of complicated grief. http://www.mayoclinic.com/health/complicatedgrief/DS01023/DSECTION=symptoms
- Professional support is needed when:
  - Trouble functioning at home or work after an extended period of time • Suffering from severe fear, anxiety, or depression
  - Unable to form close, satisfying relationships
  - Experiencing terrifying memories, nightmares, or flashbacks
  - Avoiding more and more things that are related to the trauma
  - Emotionally numb and disconnected from others
  - Using alcohol or drugs to feel better
- Educate the family on the various ways of coping and living after the death of a child. Underscore how important it is for them to utilize resources to assist in finding productive ways to cope. There are countless ways for families to cope with their grief in a positive way, including but not limited to; participating in support groups, memorializing their child, fundraising for a cause to prevent future deaths, and pursuing legislative advocacy.
- Reduce their isolation and confusion by connecting them with SUDC specific resources in the SUDC program where their honest feelings can be shared openly, in addition to local Non-SUDC specific bereavement resources.

Resources for meeting the emotional needs of the bereaved:

- Scientific Working Group for Medicolegal Death Investigation's Principles for Communicating with Next of Kin during medicolegal Death Investigations. Published June 2012
- National Center for Post Traumatic Stress Disorder - http://www.ptsd.va.gov/
- The Complicated Grief Program at Columbia University – http://www.complicatedgrief.org/
- American Psychiatric Association- www.psychiatry.org
- National Center for Post Traumatic Stress Disorder - http://www.ptsd.va.gov/
- EMDR International Association (EMDRIA): Lists approved training programs, and a database of its certified members for client referrals.

With continued research, we hope to further refine this information to provide the best care and hope for the future of all families. The SUDC Foundation offers the above information as a starting point for

discussions with your personal doctor, who knows your family best. It is not meant to be sufficient for any specific family who has suffered an unexplained death due to some of the reasons mentioned at the beginning of this document.

Discuss the above with your doctor. Ask him/her to evaluate this information in the context of the specific outcome of the postmortem investigation in the child who died suddenly and any pertinent family history. If additional clarification or assistance is needed for understanding this document, please contact The SUDC Program for the direct contact information of the contributing professionals.

We are extremely grateful for the following professionals who helped make this document possible.

- Dominic Abrams MD MRCP, Department of Cardiology, Cardiac Arrhythmia Service, Children's Hospital of Boston, Boston, MA.
- Michael Ackerman, MD, Ph.D., Director, Long QT Syndrome Clinic, Mayo Clinic, Rochester, MN
- Michael J. Bennett PhD, FRCPath, FACB, Director, Metabolic Disease Laboratory, The Children's Hospital of Philadelphia, Philadelphia, PA
- Henry Krous, MD, Director of Pathology, Children's Hospital-San Diego, Director, San Diego SIDS/SUDC Research Project, Children's Hospital San Diego, San Diego, CA
- Lisa Marain, MSW, LCSW, former SUDC Support Services Coordinator, The SUDC Program of the CJ foundation, Hackensack, NJ
- Annapurna Poduri, MD, MPH, Assistant in Neurology, Division of Epilepsy and Clinical Neurophysiology, Children's Hospital of Boston, Boston, MA
- Piero Rinaldo, MD, Ph. D. Professor of Laboratory Medicine, Director of the Biochemical Genetics Laboratory, Mayo Clinic, Rochester, MN