

VIEWPOINT

Sudden infant death syndrome: Do ion channels play a role?

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It has been more than 30 years since an association between sudden infant death syndrome (SIDS) and abnormal cardiac repolarization was first postulated.^{1,2} Enormous advances in our clinical understanding of heritable arrhythmia syndromes (aka “the cardiac channelopathies”), our scientific understanding of ion channels and how mutant ion channels impart their proarrhythmic phenotype to the patient, and our laboratory techniques, which include high-throughput mutational analysis, have given us the tools to begin to dissect a complex, multifactorial disease such as SIDS. Now, a clearer picture of how cardiac channelopathies can create the pathogenic substrate for sudden death during the first year of life as well as the prevalence of channelopathic SIDS among autopsy negative sudden infant deaths is emerging. This review highlights the substantial progress that has been made over the last decade, in particular highlighting the most recent findings that solidify the role that ion channels play in SIDS.

Sudden infant death syndrome

SIDS is defined currently as the sudden death of an infant under the age of 1 year that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of clinical history.³ SIDS is a complex syndrome with multifactorial etiologies. Since the term was first coined in 1969, SIDS continues to be a diagnosis of exclusion. This has resulted in some controversy, with some using the diagnosis too liberally and others too infrequently. Current data suggest that approximately 60% to 80% of deaths occurring in infants younger than 1 year remain autopsy negative^{4,5}; thus, for both clinical case management and for research purposes, a more rigorous definition of SIDS was sought. To this end, a panel of experts sponsored by the CJ Foundation for SIDS was assembled in January 2004 to propose an expanded algorithm for labeling an autopsy

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negative infant death as SIDS. These suggested criteria are adapted from the resulting 2004 publication in the journal *Pediatrics* and are given in [Table 1](#).³

Epidemiologically, SIDS deaths spare the perinatal period and peak in the range from 2 to 4 months, tend to spare some months, and bear some association with minor viral infections and prematurity.⁶ Numerous environmental risk factors also abound, including maternal factors (e.g., smoking, alcohol use, low socioeconomic status, intrauterine hypoxia) and infant factors (e.g., male sex, prone sleeping, sharing of bedding with parents or siblings).⁷ Efforts such as the 1992 “Back-to-Sleep” campaign focused on these modifiable environmental risk factors, particularly avoiding the prone sleep position. These actions produced unequivocal success, as the prevalence of SIDS decreased from 1.2 per 1,000 live births in 1992 to 0.546 per 1,000 live births in 2006, a reduction of more than 50%, similar to reductions seen in Canada and many other countries.^{7,8} However, despite these efforts to address environmental factors, more than 2,200 infants died of SIDS in 2004, and it appears that the recently witnessed reductions in deaths are leveling off.⁷ In addition, SIDS rates for certain ethnicities are noticeably higher. SIDS rates among infants born to African Americans and American Indian mothers are 2.1 and 1.9 times higher than the rates for white mothers.⁸ Taken together, these data suggest that SIDS has a strong genetic component in addition to any exogenous stressors confronting infants during the first year of life.

In support of a genetic component, a number of studies have examined possible genetic causes of SIDS, including the serotonergic pathway^{9–11} and fatty acid oxidation pathways.¹² However, a growing body of work has implicated the cardiac channelopathies, particularly long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome, in which mutations in critical cardiac ion channels and their interacting proteins can result in a host vulnerable to sudden death at any age, including infancy.

Cardiac channelopathies and sudden death

More than 30 years ago, both Drs. Schwartz and Maron proposed a link between LQTS and SIDS, the first such channelopathy to be implicated in this syndrome.^{1,2} LQTS affects approximately 1 in 2,500 individuals,¹³ causing a hallmark prolongation of the QT interval on ECG. LQTS

Table 1 Classifications of sudden infant death syndrome (SIDS)

General Definition of SIDS: Sudden unexpected death of an infant under the age of 1 year, with onset of fatal episode appearing to occur during sleep that remains unexplained after a thorough investigation, including complete medical autopsy and review of both the circumstances surrounding death and the clinical history.

Category IA SIDS ("Classic SIDS")

Criteria: Must fit general definition above and satisfy the requirements of each category stated below:

Clinical

- Age at death >21 days but <9 months
- Normal clinical history, including term pregnancy (gestational age ≥ 37 weeks) and normal growth and development
- No similarly unexplained deaths among siblings or other close genetic relatives (uncles, aunts, or first-degree cousins) or of other infants in custody of same caregiver

Circumstances of Death

- Investigation of the various scenes where incidents contributing to death might have occurred does not provide any explanation for the death
- Sleeping environment deemed safe, with no evidence of accidental death

Autopsy

- Negative

Category IB SIDS

Criteria: Satisfies general definition and category IA requirements, except that investigation of the circumstances of death did not occur and/or autopsy was incomplete.

Category II SIDS

Criteria: Satisfies Category I criteria except for ≥ 1 of the following:

Clinical

- Age falls outside range for "classic SIDS"
- History of similar deaths (see above) but not considered infanticide or resulting from a known genetic disorder
- Neonatal or perinatal conditions that have resolved by time of death

Circumstances of Death

- Asphyxia or suffocation not completely ruled out

Autopsy

- Abnormal but inconclusive

Unclassified Sudden Infant Death

Criteria: Does not meet criteria for category I or II, but alternative diagnoses are equivocal. Includes cases for which autopsies were not performed.

Postresuscitation Cases

Criteria: Infant found in extremis, resuscitated, and later died. May be included in previous categories depending on fulfillment of aforementioned criteria.

Adapted from Krous et al.³

most often manifests clinically as syncope, seizures, or sudden death due to its trademark arrhythmia torsade de pointes.¹⁴ LQTS can be inherited or acquired, with the two inherited forms of LQTS being the extremely rare autosomal recessive Jervell and Lange-Nielsen syndrome with accompanying sensorineural hearing loss, and the more common autosomal dominant Romano-Ward syndrome. To

date, 12 genes have been implicated in LQTS, with approximately 75%^{15,16} of LQTS classified as LQT1 (mutations in the *KCNQ1*-encoded potassium channel),¹⁷ LQT2 (*KCNH2*-encoded potassium channel),¹⁸ or LQT3 (*SCN5A*-encoded sodium channel).¹⁹

The genotypes for a small proportion of the remaining 25% of affected individuals are being exposed gradually. Although most of this subset remains genotype negative, mutations occurring at 1% frequency have been identified in a variety of ion channels or channel interacting proteins: cytoskeletal protein ankyrin B (LQT4),²⁰ *KCNQ1* beta-subunit minK (LQT5),²¹ HERG beta-subunit MiRP1 (LQT6),²² potassium channel Kir2.1 (LQT7),²³ L-type calcium channel (Timothy syndrome/LQT8),²⁴ caveolin-3 (LQT9),²⁵ beta4 subunit of the sodium channel (LQT10),²⁶ *AKAP9*-encoded adaptor protein yotiao, which interacts with *KCNQ1* (LQT11),²⁷ and cytoskeletal sodium channel regulator α_1 -syntrophin (LQT12).²⁸

In contrast to LQTS, Brugada syndrome was first described in 1992 by Pedro and Josep Brugada as a new distinct clinical entity that included persistent ST-segment elevation, right bundle branch block, and a high incidence of sudden cardiac death,²⁹ particularly in Asia, where it manifests as sudden unexpected nocturnal death syndrome, the most common cause of natural death in young Asians.³⁰ Brugada syndrome can manifest in early childhood and has been diagnosed in infants as young as 2 days.³¹ Genetically, "loss-of-function" mutations in the *SCN5A*-encoded cardiac sodium channel are the most common explanations (20%–30%) for Brugada syndrome.³¹ More recently, a mutation in the gene *GPD1L* encoding the enzyme glycerol-3-phosphate dehydrogenase-1-like that resulted in Brugada syndrome in a large multigenerational family with the disease³² and a "loss-of-function" *SCN5A* phenotype was described. In addition to the sodium channel, Antzelevitch et al³³ also recently implicated "loss-of-function" mutations in the alpha- (*CACNA1C*) and beta-subunits (*CACNB2b*) of the L-type calcium channel as novel causes of Brugada syndrome.

CPVT is another cardiac channelopathy characterized by polymorphic ventricular tachycardia in the presence of adrenergic stimuli, particularly manifesting in childhood and adolescence as syncope or sudden death during exertion, extreme stress, or emotion.^{34,35} Rare cases of resuscitated cardiac arrest and sudden cardiac death occurring during sleep in patients with CPVT have been reported.^{36,37} Most often, CPVT is an autosomal dominant disease. It is characterized by mutations in the *RYR2*-encoded cardiac ryanodine receptor/calcium release channel,^{38,39} which is the major regulator of calcium release from the sarcoplasmic reticulum during the plateau of the action potential. A recessive form of CPVT is caused by homozygous mutations in *CASQ2*-encoded calsequestrin, the major calcium-binding protein within the lumen of the sarcoplasmic reticulum. It is associated with more severe symptoms and earlier disease onset.³⁵

Channelopathies and SIDS

The 1976 hypothesis that abnormal cardiac repolarization stemming from LQTS might play a role in SIDS was advanced in 1998 by the publication of a monumental 19-year prospective study of more than 34,000 infants, recording ECGs on the third or fourth day of life.⁴⁰ Significantly, the 24 infants who died during the first year of life and were rendered a diagnosis of SIDS demonstrated a corrected QT interval (QTc) that was significantly longer than in either those infants who died of other causes or those who survived. In fact, 12 of the 24 SIDS victims had a QTc exceeding 440 ms, the 97.5th percentile for the entire population of 3- and 4-day-old infants.

Quite expectedly, this article generated a large amount of controversy among the pediatric community and resulted in an entire editorial section of *Pediatrics* entitled "Comments on a Sudden Infant Death Article in Another Journal" dedicated to expressing concern over these remarkable and disturbing findings.⁴¹ Central to the strong response was concern over instituting a widespread ECG neonatal screening program with a QTc cutoff of 440 ms. In the current study, this would have detected 861 healthy infants who did not die of SIDS (a positive predictive value of 1.4%), potentially subjecting these healthy infants to unnecessary treatment and their parents to unnecessary angst.

However, what was lost in the controversy on how to implement such findings was what Schwartz et al⁴⁰ had demonstrated convincingly: that abnormally delayed cardiac repolarization, whether directly reflecting the presence of a primary channelopathy or indirectly reflecting autonomic instability, may be signaling an at-risk infant and a SIDS-vulnerable host. What the study convincingly demonstrated was that infants with a day 3/day 4 QTc greater than 440 ms had an odds ratio for SIDS of 41.3 (47 for boys),⁴⁰ an odds ratio significantly greater than nearly all the known environmental risk factors for SIDS such as cigarette smoke exposure or prone sleeping position. The results of this profound study certainly demanded further exploration into a causal link between SIDS and LQTS.

Two years later, Schwartz et al⁴² extended the chain of evidence toward a primary channelopathic cause of some cases of SIDS, with a proof-of-principle case of resuscitated sudden death during the first year of life. They reported a 44-day-old infant who presented to the emergency room cyanotic and pulseless and was defibrillated successfully from ventricular fibrillation. Episodes of torsade de pointes and a prolonged QTc of 648 ms, both hallmark signs of LQTS, were documented, and a combined therapy of propranolol and mexiletine was begun, which alleviated symptoms during 5-year follow-up. A sporadic mutation in the LQT3-associated cardiac sodium channel gene *SCN5A* was identified that resulted in the LQT cellular phenotype of increased late sodium current when expressed in a heterologous overexpression system. Given a negative family history and normal QT intervals in both parents, this child most

certainly would have been rendered a postmortem label of SIDS had resuscitation efforts failed.

This study was followed by two anecdotal reports of molecular autopsies linking LQTS genes with infant death. The first was a 9-week-old with a premortem diagnosis of LQTS, a documented QTc greater than 600 ms, and a history of oral propranolol therapy (5 mg/kg/day) who was unsuccessfully resuscitated from sudden cardiac arrest by the parents. Molecular autopsy of the LQTS genes located the *SCN5A* mutation A1330P, which upon functional characterization in a heterologous system demonstrated a LQT3 phenotype.⁴³ The second, also reported by Schwartz et al, was a true SIDS case in an Italian family that contained the same *KCNQ1* mutation, P117L, as in a classic LQT1 multigenerational family.⁴⁴

Ackerman et al⁴⁵ subsequently performed the first systematic postmortem genetic testing of *SCN5A* in a population-based cohort of SIDS. Two missense mutations, A997S and R1826H, were discovered in two of the 58 white SIDS victims but absent in 800 reference alleles. Both mutations demonstrated delayed channel inactivation kinetics and a twofold to threefold increase in late sodium current.⁴⁵ This same population-based cohort was examined for potassium channel variants and two additional potentially pathogenic mutations were identified: a white infant with G294V-KCNH2 and an African-American infant with five different channel variants including T600M-KCNQ1 and V14I-KCNE2.⁴⁶

Arnestad et al⁴⁷ replicated these findings in a separate cohort of 201 Norwegian SIDS cases. They examined seven LQTS susceptibility genes and reported a 9.5% (19/201) prevalence of functionally significant rare genetic variants. The vast majority of these mutations were identified in the major LQTS susceptibility genes *KCNQ1*, *KCNH2*, and *SCN5A*. The same group also functionally characterized the eight previously uncharacterized rare variants identified in *SCN5A*. This elegant study demonstrated that 5 of the 8 variants had increased LQT3-like late sodium current. The other three variants also displayed increased late current under various conditions.⁴⁸ Some of the potassium channel variants also displayed functional impairment.⁴⁹

Overall, these findings indicated that (1) approximately 10% of SIDS may emanate from LQTS-causing mutations and (2) the cardiac sodium channel assumes a prominent position in channelopathic SIDS. Table 2 gives a current list of channelopathy genes implicated in SIDS pathogenesis. Although mutations in *SCN5A* account for only approximately 10% of LQTS cases, *SCN5A* provided half of the rare genetic variants found in the Norwegian cases, and all of these had functional phenotypes. Consequently, a sodium channel-centric view of channelopathic SIDS is emerging, and all of the channel interacting proteins of the NaV1.5 macromolecular complex are being scrutinized carefully for possible SIDS-associated mutations.

Mutations in the LQT9-susceptibility gene (*CAV3*), which encodes caveolin-3,²⁵ have been found among Afri-

Table 2 Channelopathy genes implicated in pathogenesis of sudden infant death syndrome

Gene	Channelopathy genotype	Reference
<i>CAV3</i>	LQT9	50
<i>GPD1L</i>	BrS2	51
<i>KCNE2</i>	LQT6	47
<i>KCNH2</i>	LQT2/SQT1	47, 49
<i>KCNQ1</i>	LQT1/SQT2	44, 47, 49
<i>RYR2</i>	CPVT1	34
<i>SCN5A</i>	LQT3, BrS1	42, 43, 45, 47

BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; LQT = long QT syndrome.

can-American SIDS cases.⁵⁰ Three of 50 African-American infants had *CAV3* missense mutations that confer pathologic late sodium current properties to an otherwise intact pore-forming *SCN5A*-encoded alpha-subunit. This study was the first to implicate a sodium channel interacting protein in the pathogenesis of SIDS. Whether SIDS-associated mutations will be discovered among the other sodium channel interacting proteins (beta4 subunit [LQT10] and α 1-syntrophin [LQT12]) that recently have been identified as novel pathogenic substrates for LQTS remains to be determined.^{26,28}

Mutations in the newly described Brugada syndrome susceptibility gene³² *GPD1L*, which encodes the glycerol-3-phosphate dehydrogenase 1-like protein, have been detected in 1% of SIDS cases.⁵¹ In contrast to the acquired “gain-of-function” to the sodium channel by the caveolin-3 mutations, the SIDS-associated *GPD1L* mutations conferred a profound “loss-of-function” in terms of peak sodium current density when expressed with an otherwise intact sodium channel alpha-subunit. *GPD1L*-SIDS would be expected to culminate in a Brugada syndrome-like lethal ventricular arrhythmia.

Extending beyond surface ion channels, mutations in the ryanodine receptor/calcium release channel that localizes to the sarcoplasmic reticulum of the cardiomyocyte cause CPVT, a disease that most often presents in childhood and adolescence. A study by Tester et al³⁴ demonstrated a novel mechanism for SIDS, with the discovery of *RYR2* rare missense mutations in 1% to 2% of unrelated SIDS cases that, under conditions stimulating a stress environment, imparted a gain-of-function to the ryanodine receptor causing diastolic leak, similar to previously characterized CPVT-associated *RyR2* mutations. This study extends the diversity of channelopathic causes of unexplained death during the first year of life.

An obvious challenge to establishing causality between the presence of rare cardiac channel mutations and an infant's death is lack of documentation that the mutation-positive infant's exiting rhythm was, in fact, ventricular fibrillation. In lieu of this, it is critical for functional studies to prove not only that these mutations are rare but that they clearly perturb the physiology of the channel, consistent with established LQTS/Brugada syndrome/CPVT-linked arrhythmogenic mechanisms. Too many putative channelopa-

thy and SIDS-associated mutations have been given a “free pass” as a pathologic mutation by virtue of simply residing in a known gene previously proven to cause a particular heritable arrhythmia syndrome. The observation that 3% to 5% of healthy volunteers possess rare missense “mutations” in *SCN5A* has reinforced the mandate for careful electrophysiologic phenotyping.⁵² This necessary care is not restricted to the sodium channel. For example, a separate group in Germany surveyed 41 consecutive SIDS victims for mutations in the most common LQTS susceptibility genes. They identified one mutation (H105L-KCNQ1) in one SIDS victim. However, the “mutation” yielded a functionally normal potassium channel in two different heterologous expression systems.⁵³

Polymorphisms and SIDS

In contrast to rare pathogenic mutations in cardiac channels that serve as the *principal* substrate for approximately 10% to 15% of SIDS cases, the extent, impact, and implications of common functionally significant, nonsynonymous single nucleotide polymorphisms (SNPs) as sudden death predisposing SNPs during the first year of life are less clear. Take, for example, S1103Y-*SCN5A*, a relatively race-specific common SNP present in more than 10% of the African-American population. In 2002, Splawski et al⁵⁴ discovered that S1103Y-*SCN5A* (denoted previously as S1102Y), with a prevalence of 13% among African Americans, was associated with a markedly increased risk (odds ratio 8.7) for arrhythmia susceptibility, particularly in the context of other acquired risk factors such as medications, hypokalemia, and structural heart disease. Subsequently, Burke et al⁵⁵ observed significant overrepresentation of the S1103Y polymorphism among African-American adolescents and adults whose deaths were classified as autopsy negative sudden unexplained death.

Plant et al⁵⁶ reported an overrepresentation of S1103Y homozygotes (YY) in a large cohort of African-American SIDS cases (n = 133), suggesting a 24-fold risk for SIDS in infants who are homozygous for the Y1103-encoding allele (YY genotype). Additionally, although wild type-like under normal conditions, the S1103Y-containing sodium channel transformed into a channel with marked accentuation of late sodium current when exposed to extracellular acidosis, thereby fulfilling the much-discussed triple-risk hypothesis of SIDS involving (1) the vulnerable host (S1103Y positive), (2) an exogenous stressor (acidosis), and (3) a critical development period (the first year of life).⁵⁶ Finally, we completed the fourth independent study of S1103Y and African-American infants showing a marked overrepresentation of S1103Y among African-American SIDS cases (22.5% heterozygote) compared with its anticipated heterozygous frequency (10%–15%).⁵⁷

Another possible functionally significant sodium channel polymorphism is V1951L-*SCN5A*.⁴⁸ When expressed in the setting of the most commonly spliced *SCN5A* transcript that lacks a glutamine at position 1077 (Q1077del-*SCN5A*), V1951L yields a sodium channel with increased late sodium

current. V1951L initially was reported as a Brugada syndrome mutation.⁵⁸ Subsequently it was described in 1 of 201 of SIDS cases and was absent among the Norwegian controls. However, the ethnicity of the SIDS cases was not stated explicitly. Although rare among other ethnicities, V1951L is a common polymorphism among Hispanics, with a heterozygous frequency of 7%.⁵² Like S1103Y, V1951L may be a sudden death predisposing, proarrhythmic polymorphism.

Translating these bench discoveries to the cribside: Implications for the future

Despite these foundational scientific breakthroughs over the past decade, translation of the two fundamental discoveries that (1) 10% to 15% of SIDS may be channelopathic and (2) common cardiac channel SNPs may confer risk for sudden death at any age, including infancy, is extremely complicated. Regarding the latter, should the data regarding the proarrhythmic, sudden death predisposing common sodium channel SNP S1103Y compel routine genetic testing of all African Americans in order to identify the 10% to 15% who host this polymorphism? How would these S1103Y-positive African-American infants be monitored differently? Here is where relative risk and absolute risk collide. Despite an impressive odds ratio greater than 8 (arguably one of the highest odds ratios or relative risks that we may see for SNPs) for increased sudden death susceptibility, the vast majority of the estimated 60,000 to 90,000 S1103Y-positive African-American infants born each year will not succumb to unexplained sudden death during the first year of life because of S1103Y's proarrhythmic potential (overall <1,000 African-American SIDS cases per year in the United States).⁵⁷ Perhaps the data instead should suggest consideration of the merits of targeted preprescription genotyping of African Americans prior to their receiving medications that have the potential for an unwanted QT-prolonging side effect. Although how Y1103 would induce arrhythmia in the setting of QT-prolonging agents is unclear and no direct association with Y1103 and drug-induced torsade de pointes has been documented, action potential simulations have demonstrated abnormal repolarization and early afterdepolarizations in the setting of concomitant HERG potassium channel blockade, the most common mechanism of drug-induced LQTS.⁵⁴

With respect to the former discovery, what actions should be stimulated by the knowledge that 10% to 15% of SIDS cases may stem from the presence of rare, pathogenic, channelopathic mutations? Universal genetic testing? Although it readily comes to mind, such an endeavor is not yet ready for prime time. Many of the SIDS-associated channel genes have not been included in commercially available genetic tests thus far. Because CPVT mutations have been discovered as well, a combined LQTS and CPVT panel would have to be conducted, possibly in a tiered strategy. Several additional difficulties with universal screening immediately surface. For example, in the case of S1103Y-SCN5A, more than 10% of the 616,000 African-American

infants born every year⁸ would test positive, with the vast majority destined for a life free of a primary channelopathy-induced arrhythmia or sudden cardiac death. Moreover, the observation that 3% to 5% of otherwise healthy adult volunteers nevertheless host a rare variant in *SCN5A*, the gene most often implicated in channelopathic SIDS, further complicates the issue.⁵² Although current data are beginning to elucidate which mutations are functionally relevant and indeed pathogenic, this complex issue of distinguishing true mutations from so-called background genetic noise must be deciphered before a genetic test can be implemented effectively and universally among infants.

Perhaps the most immediate way forward is implementation of new "standards of care" for the victims and families of SIDS. The current data argue that postmortem genetic testing of a SIDS victim makes sense as part of the infant's comprehensive autopsy. However, even though probably more cost effective in the long run, insurance companies currently are reluctant to pay for anything after an infant dies. What about postmortem surveillance ECGs of the infant's surviving parents and siblings? Importantly, because of the anonymized study design of several of the SIDS-channel investigations, the relative percentage of familial channel mutations versus sporadic mutations among channelopathic SIDS remains unknown. However, taking these findings together, it seems reasonable to recommend a 12-lead ECG recording for first-degree relatives of a SIDS victim to further investigate the possibility of familial LQTS. However, it must be stressed that such an approach would not provide an effective screen for CPVT, which would require at least a treadmill exercise stress test to detect at-risk family members.

Then what about the charged issue of universal ECG screening during infancy for the early detection of a potentially lethal, highly treatable condition such as LQTS? Even if the previously mentioned improvements in standards of care following the death of an infant occur, universal ECG screening during infancy is an issue that *must* be contemplated because of the discoveries of the past decade. Presently, the only possible screening test for LQTS would be the 12-lead ECG. The issues and challenges of screening for such a disease in an asymptomatic population would be numerous: timing of QTc assessment (probably 2–4 weeks of age rather than the first week of life), the QTc cutoff value for adequate sensitivity (probably 460–470 ms), false-positive results, quality control regarding QTc interpretation, and that much beloved cost-effectiveness query. In addition, although the treatment of choice for clinically diagnosed LQTS involves beta-blocker pharmacotherapy, LQT3, which the current SIDS datasets argue would account for at least half of channelopathic SIDS, may not be amenable to beta-blockers. Although anecdotal evidence suggests a combination of mexiletine and propranolol may be effective for refractory LQT3,⁵⁹ the best therapeutic approach for the asymptomatic infant who tests positive for LQT3 is unclear. Nevertheless, it should be undeniable that

a highly treatable, potentially lethal condition affecting 1 in 2,500 persons (i.e. LQTS) *deserves* consideration for screening, especially when several states screen for “rare as hen’s teeth” entities such as maple syrup urine disease and every state screens for phenylketonuria. At issue should not be whether screening for LQTS is meritorious or worthy but whether a suitable screening test for LQTS and subsequent treatment plan yet exists.

Finally, progress in the epidemiology of channelopathic SIDS and identification of the at-risk infant is contingent on the full adoption of rigorous criteria for proper categorization of an infant’s death. Considering the expanded algorithm given in Table 1, deaths stemming from a previously unrecognized and therefore undiagnosed channelopathy, such as those listed here, or any other heritable genetic defect might have fallen under a category II SIDS designation had past medical history and family history been more rigorously ascertained. Future genetic studies comparing classic (category I) and atypical (category II) SIDS may elucidate this distinction further. Hopefully, widespread implementation of the diagnostic criteria listed in Table 1 will further advance the dissection of the pathogenetic mechanisms responsible for sudden death during infancy.

Conclusion

Compelling molecular, electrophysiologic, and epidemiologic evidence now exists to conclude that approximately 10% to 15% of autopsy negative SIDS cases stem from cardiac channelopathies, chiefly long QT syndrome and often through perturbations of the sodium channel NaV1.5 macromolecular complex. Although novel channelopathic causes of SIDS certainly await discovery and our understanding of the significance (or lack thereof) of proarrhythmic channel SNPs requires further maturation, the time has come for the fundamental discoveries of the last decade to translate into innovative strategies to detect and protect the at-risk infant and his/her family members during this next decade.

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