Sudden infant death syndrome and cardiac channelopathies: from mechanisms to prevention of avoidable tragedies

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Abstract

The sudden infant death syndrome (SIDS), with the load of mystery surrounding its causes and with the devastating impact on the affected families, remains the greatest contributor to post-neonatal mortality during the first year of life. Following a succinct review of the non-cardiac genetic factors, which have been associated with SIDS, we focus on the cardiac hypothesis for SIDS and specifically on those diseases produced by cardiac ion channel mutations, the so-called channelopathies. Special attention is devoted to the fact that these causes of SIDS, and especially the long QT syndrome, are preventable if diagnosed in time. This highlights the importance of neonatal ECG screening and carries a number of practical implications, including medico-legal considerations.

Introduction

Sudden infant death syndrome (SIDS) remains the leading mortality cause in the first year of life, following the first week. The mystery surrounding these deaths, the fact that diagnosis is usually one of exclusion, that these are sudden and unexpected deaths of infants thought to be healthy, all contributes to the devastating psychological impact on families and to the unjustified but never ending guilty feelings of the mothers of SIDS victims.1

SIDS has been referred to as a disease of theories because of the large number of hypothe-

Overview of sudden infant death syndrome

The transition in the approach to SIDS has been marked by the changes in its definition. At the time of the Seattle conference in 1970 Beckwith4 provided its first classic definition: SIDS is the sudden death of any infant or young child which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death. This definition remains valid despite the subsequent addition of specifications such as limiting the victim's age to < 1 year, specifying that death occurred apparently during sleep, and also a review of the death scene, and clinical history.5,6 An algorithm for labeling as SIDS an autopsy-negative infant death has also been proposed6 (Table 1).

Progressively it has been accepted the concept that SIDS is a multifactorial disease. This brings in two concepts: one is that infants may die suddenly because of several different causes and the other is that multiple factors, by themselves insufficient, may act synergistically to create a deadly situation, the so-called triple risk hypothesis.7 The latter is based on the simultaneous and synergistic presence of three risk factors contributing to SIDS, namely a vulnerable infant, a critical developmental period in homeostatic control, and an exogenous stressor. In 2001 the National Institute of Child Health and Development SIDS Strategic Plan stated that Infants who die from SIDS have abnormalities at birth that render them vulnerable to potentially life-threatening challenges during infancy.8 This suggested that SIDS should be regarded as a developmental disorder originating during fetal development. However, none of the proposed multiple risk hypotheses have significantly modified or improved our understanding of the pathogenesis of SIDS.

In 1992, based on the hypothesis that prone sleep could be an exogenous stressor, the American Academy of Pediatrics recommended that babies sleep in the supine position and led to the enthusiastically accepted international Back-to-Sleep campaign.9 The campaign in the USA and in several other countries was associated with markedly reduced SIDS rates, from 1.2 per 1000 live births in 1992 to 0.55 per 1000 live births in 2006.10 It appears that these recently observed reductions in SIDS deaths are leveling off.10 There are several considerations, usually underreported, that might limit the enthusiasm for the actual effectiveness of placing infants in the supine position. The fact that a campaign is initiated, does not mean at all that most of the mothers living in any given country actually follow it, and this lack of adherence to recommendations and guidelines is always higher in the lower socio-economic strata in which the incidence of SIDS is higher. This suggests the possibility that the reduction certainly observed in SIDS prevalence might depend, at least in part,
also on other factors and that the relationship between the campaign and the SIDS reduction might represent more an association than a causal effect. An important one is that the changes in definitions of SIDS have apparently simply shifted some of these deaths under different codes.12 Finally, in some countries, like Italy, in which the Back-to-Sleep campaign started (as usual) with considerable delay, the reduction in the prevalence of SIDS had occurred before the campaign was actually initiated.13 There are ethnic-specific disparities in rates14 as they are twice as high among infants of Afro-American than of Caucasian mothers;15 high risk is also observed among American Indians and Maoris.16 SIDS is markedly lower among Asian infants. These data suggest the existence of population-specific genetic backgrounds.

Several non-cardiac genetic mechanisms have been postulated for SIDS and they essentially involve infective, autonomic, and metabolic genetic factors. They are reported here briefly because for none of them adequate quantification and clear-cut evidence exists and because the mechanisms proposed leave very little opportunity for prevention.

The association between SIDS and infections is largely based on the concept that potentially pathogenic toxins causing a overwhelming immunologic response through pro-inflammatory cytokine release would ultimately cause physiological changes that lead to the unexpected death of an apparently healthy infant.17 The supporters of this hypothesis give weight to the evidence that several immunologic polymorphisms modulating the inflammatory responses have been identified more frequently in SIDS victims than in controls. Down-regulation of the anti-inflammatory pathway through cytokine interleukin-10 (IL-10), as well as overexpression of the cytokines IL-1β and IL-6 and elevated vascular endothelial growth factor, have been associated with SIDS.18,19

Impaired autonomic regulation, with structural and neurotransmitter alterations in the brainstem, has been postulated as another mechanism based on post-mortem findings in cases of SIDS. The main focus has been on serotonin, a central nervous system neurotransmitter involved in respiratory and cardiovascular pathways. The idea would be that a serotonergic dysfunction might prevent the physiological protective respiratory and autonomic responses to life-threatening hypoxia or hypercapnia during sleep, ultimately leading to SIDS.19,20 As a matter of fact, a polymorphism in the variable tandem repeat sequence of the promoter region of the serotonin transporter (5-HTT) gene, which is expected to decrease the serotonin level at synapses, was found to be more often present in SIDS cases than controls.20

Through postmortem biochemical screening of livers from SIDS cases, Boles et al. found abnormalities in specific fatty acid oxidation pathways.21 Attention has thus been paid to medium-chain acyl-CoA dehydrogenase (MCAD) deficiency which is a metabolic disorder previously associated to a few SIDS cases. This autosomal recessive inherited disease is caused by a deficiency in the enzyme which catalyzes the first step in oxidation of fatty acids. A number of studies tested SIDS cases for the missense mutation A985G, the most prevalent genetic variant causing MCAD deficiency, but with negative results in very large case-control studies involving more than 2500 cases and 4500 controls.22 Two key enzymes in blood glucose homeostasis were also investigated, and whereas low hepatic glucose-6-phosphatase was found in SIDS cases, no similar evidences were found for glucokinase.23,24

The studies just mentioned indicate that the quest for the causes of SIDS is fairly extended. However, most if not all of these studies suffer from significant limitations either in design or more often in the difficulty to explain, based on the mechanisms proposed, the sudden and often almost instantaneous death of an infant regarded as essentially healthy until a few moments earlier. From a conceptual point of view, the interested reader will find rational discussions about the problems with most of the theories presented about SIDS in previous essays.23 Critical, among these limitations, is the paucity of controls and the excess number of SIDS victims who had come to medical attention because of episodes of apnea and are thereby biasing the findings toward respiratory mechanisms.

The situation is quite different for studies which have examined the so-called cardiac

### 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** |
| i Age at death > 21 days but < 9 months; |
| ii Normal clinical history, including term pregnancy (gestational age ≥ 37 weeks) and normal growth and development; |
| iii 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** |
| i Investigation of the various scenes where incidents contributing to death might have occurred does not provide any explanation for the death; |
| ii Sleeping environment deemed safe, with no evidence of accidental death. |
| **Autopsy** |
| i 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** |
| i Age falls outside range for “classic SIDS”; |
| ii History of similar deaths (see above) but not considered infanticide or resulting from a known genetic disorder; |
| iii Neonatal or perinatal conditions that have resolved by time of death. |
| **Circumstances of death** |
| i Asphyxia or suffocation not completely ruled out. |
| **Autopsy** |
| i 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. |

| Post-resuscitation cases |
|--------------------------|
| **Criteria:** Infant found in extremis, resuscitated, and later died. May be included in previous categories depending on fulfillment of aforementioned criteria. |

From Van Norstrand et al.25
Cardiac channelopathies in sudden infant death syndrome

In 1976, first Schwartz and then Maron et al. proposed a link between LQTS and SIDS. LQTS is a well investigated cardiac arrhythmia syndrome of genetic origin typically characterized by a prolongation of the QT interval on the electrocardiogram (ECG) and by the occurrence of syncope or cardiac arrest, mostly precipitated by emotional or physical stress but also occurring at rest and during sleep according to gene specific triggers. LQTS is not rare as it affects approximately 1 in 2000 Caucasian individuals.

Following the 1976 hypothesis Schwartz et al. designed and implemented a prospective study of neonatal electrocardiography with the objective of acquiring ECGs for the measurement of the QT interval in a very large number of apparently healthy infants and to follow them prospectively for the unavoidable occurrence of SIDS in some of them. The Milan Prospective Study was an 18-year long study, which enrolled over 33,000 infants with an objective of acquiring ECGs for the measurement of the QT interval in a very large number of apparently healthy infants and to follow them prospectively for the unavoidable occurrence of SIDS in some of them. The study found that 12 of the 24 infants classified as SIDS victims had a QTc exceeding 440 ms (2 standard deviations above the mean and representing the upper limit of normal values), a QTc value exceeding the 97.5th percentile for the entire population of 3- and 4-day-old infants. The risk of SIDS for infants with a QTc > 440 ms was 41 times greater than that for infants with a normal QTc, as the odds ratio (OR) was 41.3, 95% CI 17.3-98.4. A prolonged QTc was a risk factor far exceeding all traditional risk factors for SIDS.

While these data were strongly suggestive, they had not produced the actual evidence that LQTS was causing SIDS because, despite the prolonged QT interval in several SIDS victims, the nature of the study prevented the actual evidence that the victims were indeed affected by LQTS. Proof-of-concept was still necessary.

This came in year 2000, when we described the case of a 44-day-old infant found cyanotic, apneic and pulseless, and rushed by the parents to a nearby hospital where the presence of ventricular fibrillation was demonstrated. After defibrillation the ECG showed clear signs of LQTS (Figure 1), i.e. a marked prolongation of the QT interval and T wave alternans. Following the diagnosis of LQTS and initiation of therapy we were asked to perform molecular screening which identified a de novo missense mutation in the cardiac sodium channel gene (SCN5A), carried by the infant and not by his parents who had a normal QT interval.

This infant represented a typical case of near-SIDS, since the documented ventricular fibrillation would have unavoidably caused his sudden death, which was avoided only by the prompt defibrillation. It is also evident that if the child had died, as he was meant to follow, he would have died due to ventricular fibrillation, LQTS could have not been suspected given the normal ECG and lack of LQTS mutations in both parents. This case provided the first evidence of a molecular link between LQTS and SIDS.

The demonstration that not only the sodium channel but also other ionic channels associated with LQTS might cause SIDS was provided one year later in an infant who actually died of SIDS. A de novo mutation (C350T) in the KCNQ1 gene coding for the I_Ks current was identified in this SIDS victim and its pathogenicity was supported by the identification of the same mutation in an unrelated family with several members affected by LQTS.

Three are the genes (KCNQ1, KCNH2, SCN5A) implicated in most cases of LQTS and of SIDS as well. Also minor LQTS genes have been implicated in SIDS (Table 2), especially those related to proteins involved in intracellular trafficking and modulation of the cardiac sodium current. Examples of anecdotal findings include α1-syntrophin (SNTA1), a structural protein forming complexes between SCN5A, nitric oxide synthase (nNOS), and plasma membrane Ca-ATPase (PMCA4b), which was associated with neonatal sudden death. A role in favoring SIDS was also found for mutations in CAV3 encoding caveolin-3, the major component of caveolae. The effect of these mutations is to increase the late sodium current compared to wild type, thus mimicking the LQT3 phenotype. Later on, in an ethnically mixed population of almost 300 SIDS, screening of sodium channel β-subunits already implicated in cardiac arrhythmic syndromes revealed in 3 SIDS victims missense substitu-

Figure 1. Electrocardiograms at the time of admission to the hospital (Panel A) and after the restoration of sinus rhythm (Panel B). At hospital admission, the 44-day-old infant had ventricular fibrillation (Panel A). After the restoration of sinus rhythm, the corrected QT interval was found to be markedly prolonged (648 ms) (Panel B), and showing clear T wave alternans. Modified from Schwartz et al.


The role of the long QT syndrome in sudden infant death syndrome

The initial, ground-breaking but anecdotal, reports linking LQTS to SIDS stimulated the design of cohort studies aiming at providing a quantification of this important phenomenon. Accordingly, two independent research groups across the Atlantic performed extensive molecular investigations in SIDS cohorts to provide a reliable prevalence of LQTS in the pathogenesis of SIDS.

The American group, led by Mike Ackerman, collected necropsic tissue from 93 infants who had died suddenly and were subsequently classified as SIDS, with a racial distribution of 58 whites, 34 blacks and 1 Hispanic. Two SCN5A variants (A997S and R1826H), not detected in 300 ethnically-matched controls, were identified respectively in a 6-week and 1-month old white males, found not breathing in bed. Functional studies performed in HEK cells showed a typical LQTS type 3 phenotype for these variants. They concluded that approximately 2% of this SIDS cohort had an identifiable SCN5A channel defect, suggesting that mutations in cardiac sodium channel may provide a lethal arrhythmogenic substrate in some infants at risk for SIDS. Next they extended the analysis to potassium channels and their subunits, identifying the KCNHa-G294V variant in a Caucasian SIDS victim, and the compound KCNQ1-T600M and KCNE2-V14I substitutions in a single Afro-American case. Overall, this small cohort (only 58 Caucasians) study identified missense mutations in 5% of Caucasians and in 3% of Afro-Americans SIDS cases, strengthening the molecular link between sudden infant death and LQTS genes.

In 2007 our group reported a genetic study performed in 201 SIDS victims. Seven LQTS genes were screened in SIDS victims, accurately categorized according to the Nordic criteria and in 182 controls all originated from the same regions in Norway. Molecular screening of the 3 main LQTS genes (KCNQ1, KCNH2, SCN5A) together with other 4 genes less commonly associated with LQTS (KCNH1, KCNE1, KCNE2, KCNJ2) was performed. All genetic variants identified in the SIDS victims and not previously investigated in vitro were tested through functional studies and only those with effects on either the sodium or the potassium current were regarded as being disease-causing. Some of the mutations exhibited significantly increased late sodium current resembling the LQTS type-3 phenotype. A second group had a smaller yet statistically significant levels of increased persistent current and another included variants with a latent functional effect, dependent on intracellular pH or on a specific splice variant. The genetic variants affecting the K+ current showed a wide spectrum of functional effects. Indeed, together with the loss-of-function mechanism typical of delayed rectifier potassium channel in LQTS, one variant (KCNQ1-E274V) demonstrated significant gain-of-function in the slow component of the K+ current. Therefore the effect of this variant is to shorten ventricular action potential, leading to a SQTS phenotype. These functional studies demonstrated that multiple alterations in cardiac ion channels may predispose to arrhythmias during post-partum and neonatal life.

Overall, this study found that genetic variants in LQTS genes were present in 9.5% of SIDS victims. There were 15 different genetic variants with a demonstrated functional effect, in 19 of the 201 SIDS cases (9.5%; 95% CI, 5.8 to 14.4%); the majority of these variants were located in SCN5A (60%), followed by KCNQ1 and KCNH2 (both 13%). Thus, based on the upper 95th percentile of the confidence intervals, up to almost 15% of SIDS can be caused by LQTS. The major role exerted by sodium channel gene mutations was confirmed in an ethnically different cohort, the 42 Japanese SIDS victims studied by Otagiri et al.

The high prevalence among SIDS victims of genetic variants in SCN5A points to the fact that mutations in the sodium channel gene are more often associated with major impairments in cardiac electrical stability and less compatible with life, a factor that might be relevant to stillbirths, as we will briefly discuss below. By contrast, most of the genetic variants in adults affected by LQTS are found in potassium channel genes, with a distribution of almost 50% for KCNQ1, 40% for KCNH2, and only 5-10% for SCN5A (Figure 2). Relevant here is the fact that SCN5A mutations are associated with lethal events more often associated with major impairments in cardiac electrical stability primarily during sleep, the condition most often associated with SIDS.
**Modifier genes and the triple risk hypothesis**

The relationship between genotype and phenotype may be not linear in inherited arrhythmia syndromes. Our group has already shown the high frequency of low penetrance in LQTS; indeed 37% of LQT1, 19% of LQT2, and 10% of LQT3 patients may have a borderline or normal QT interval. It is currently assumed that factors, either genetic or environmental, may modify the consequences of a given disease-causing mutation and either increase or decrease its pathogenicity.

In the context of SIDS we may also postulate that common but functionally relevant nonsynonymous single nucleotide polymorphisms (SNPs) may act as modifier of the arrhythmogenic risk in the first year of life, and probably later on as well. Such an effect has already been demonstrated for SNPs such as K897T in \( KCNQ1 \), \( KCNH2 \), \( H558R \) in \( SCN5A \), and as D85N in \( KCNE1 \). In our large SIDS cohort study we found that 7 of 8 SIDS victims carried the \( H558R \) common variant in association with \( SCN5A \) mutations or rare variants exhibiting only a modest or latent functional effect; indeed, the R558 allele frequency was twice as large in this subgroup of SIDS cases compared with controls.

Additionally, ethnic-specific variants may exhibit functionally relevant effect in the context of specific genetic backgrounds. Previously described examples, not reviewed in detail here for reasons of space, are those of the Afro-American polymorphism \( SCN5A-S1103Y \) and of the Hispanic polymorphism \( SCN5A-V1951L \).

Notably, the combination of pathogenic variants and/or of functional polymorphisms might trigger lethal cardiac events when combined with specific environmental factors. Such is the case of the sodium variant R680H exhibiting increased persistent current only under conditions of acidosis, as described by our group. It is of special interest here that these findings fulfill the concept of a multifactorial etiology for SIDS: as an example the triple risk factor hypothesis could be represented by a vulnerable infant (\( SCN5A-R680H \) carrier) going through a critical developmental period (the post-neonatal period) and facing an exogenous stressor (transient acidosis).

We find particularly intriguing the concept that the random but specific association between the relatively modest arrhythmic risk caused by the presence of a low-risk genetic mutation and a relatively common and usually benign genetic variant or environmental accident may result in a lethal condition. Such a combination might explain a number of SIDS cases and it highlights the play of chance.

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**From mechanisms to prevention**

A multiplicity of disorders may cause SIDS; however, for nearly all non-cardiac causes prevention is practically almost impossible. This is not the case when SIDS is caused by a lethal arrhythmia. We have shown that several channelopathies can be associated with SIDS but it is also evident that the one involved sufficiently often (10 to 15% of cases) to allow practical implications is LQTS. Two aspects are critical in terms of potential prevention: one is that LQTS is an eminently treatable disorder and its mortality has decreased from almost 60% to 1% with the introduction of effective therapies, the other is that LQTS can be rather easily recognized by a simple electrocardiogram.

The concept of neonatal ECG screening has generated many controversies but it has also been supported by the European Society of Cardiology. The relatively simple concept is that an extensive neonatal ECG screening will identify most if not all neonates affected by LQTS thus allowing early treatment with \( \beta \)-blockers and preventing sudden deaths which may occur either during the first few months of life or later on in life. Such a electrocardiographic screening has been demonstrated to be markedly cost-effective.

It stands to reason that neonatal ECG as a first line screening will allow to perform the necessary genetic screening specifically in those neonates with a twice confirmed prolongation of the QT interval. This approach has been tested in a prospective study requested and funded by the Italian Ministry of Health, following our recommendation of introducing a program of neonatal ECG screening as part of the National Health Service. This uniquely large prospective study carried out in more than 44,000 one-month-old infants demonstrated the feasibility of ECG screening in the diagnosis of most of the neonates affected by LQTS, based on ECG-guided identification of disease-causing mutations. Additionally, the study provided the first database estimation for the prevalence of the congenital LQTS and indicated that it is close to 1:2000 among Caucasians.

These data also carry a medico-legal consideration. We strongly believe that the parents of a newborn have the right to be informed that: i) a disease affecting 1 child in 2000 can kill in the first few months of life or later on; ii) effective and simple therapies exists which reduce risk to 1%; iii) the disease can be diagnosed with an ECG. Withholding this information prevents the parents from asking an ECG for their child.

We believe that post mortem genetic testing should be performed in all cases of SIDS as part of the comprehensive autopsy. We also recommend ECG screening for the first-degree relatives of a SIDS victim to investigate the possibility of familial LQTS. In case of positive genetic screening in a SIDS victim, this would guide cascade molecular screening in the family members, unmasking silent mutation carriers and allowing effective preventive measures.

Another consideration regards unexplained stillbirths, one of the most common but least studied adverse pregnancy outcomes. Stillbirths have a 6-8-fold greater incidence...
than SIDS and, according to the World Health Organization, in developed countries one in 100-200 pregnancies ends in a stillbirth. Notably, more than half of the foetal deaths after the 22nd week of gestation remain unexplained even after extensive autopsy investigation.66 Years ago we suggested a possible link among SIDS, stillbirths and LQTS.67 Our ongoing Italian study on stillbirths suggests that LQTS may contribute to more than 10% of intrauterine foetal deaths.68

Conclusions

The preceding data and related discussion conclusively show that it is no longer possible to regard SIDS, and thereby all SIDS-related sudden deaths in infancy as an unavoidable event, an act of God and cruel destiny. This is probably true for a number of them, but it is now evident that a significant portion of SIDS is due to a genetically mediated life-threatening arrhythmia which can be prevented, provided that the culprit disease is identified sufficiently early to allow protection. These are indeed preventable tragedies and this is clearly the case for LQTS, an uncommon but not rare disease for which extremely effective therapies are available. It follows that not to search for the long QT syndrome among infants, and not to alert the parents of a newborn child about this possibility, represents culpable negligence.

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