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Mini-Symposium: Sudden Infant Death Syndrome

Cardiac Abnormalities and Sudden Infant Death Syndrome

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EDUCATIONAL AIMS

- To discuss the possible role of genetic heart disease as a cause of SIDS.
- To highlight cardiac arrhythmogenic syndromes, particularly long QT syndrome, as potentially implicated in SIDS.
- To illustrate the clinical implications of a possible cardiac genetic basis in some SIDS cases.

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SUMMARY

Many factors have been implicated in SIDS cases including environmental influences such as sleeping arrangements and smoking. Most recently, cardiac abnormalities have been hypothesised to play a role in some cases, particularly the primary genetic arrhythmogenic disorders such as familial long QT syndrome (LQTS). Both post-mortem and clinical studies of SIDS cases have provided supporting evidence for the involvement of cardiac genetic disorders in SIDS. This review provides a summary of this evidence focussing particularly on the primary hypothesis related to underlying familial LQTS. In addition, the current literature relating to other cardiac genetic conditions such as Brugada syndrome (BrS) and structural heart diseases such as hypertrophic cardiomyopathy (HCM) is briefly presented. Finally, the implications of a possible cardiac genetic cause of SIDS is discussed with reference to the need for genetic testing in SIDS cases and subsequent clinical and genetic testing in family members.

INTRODUCTION

It has been suggested that cardiac abnormalities, such as the inherited primary arrhythmogenic disorders, may be implicated in a proportion of SIDS cases. Many studies have been performed, primarily focused on post-mortem genetic analyses, to determine the proportion of SIDS cases that may be attributable to an underlying cardiac genetic cause. Pathogenic (disease-causing) mutations in cardiac genes have been hypothesised to be responsible for up to 10% of all SIDS cases [1–3]. This review will examine the current literature concerned with potential cardiac related causes of SIDS, with particular reference to the development of the primary hypothesis that genetic mutations may lead to arrhythmogenic events, such as life-threatening ventricular arrhythmias, resulting in SIDS.

GENETIC HEART DISEASES

Genetic heart diseases include the arrhythmogenic conditions such as familial long QT syndrome (LQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT), as well as the structural disorders such as hypertrophic cardiomyopathy (HCM). These conditions have been shown to cause sudden death, particularly in young people aged 1-35 years [4]. In the case of the arrhythmogenic conditions, cardiac gene mutations lead to irregular cardiac ion channel function leading to arrhythmias and sudden death. In structural disorders, such as the cardiomyopathies, genetic mutations occur commonly in the sarcomere and cytoskeletal proteins leading to fibrosis and thickening of the heart muscle, providing an arrhythmogenic substrate for ventricular arrhythmias and sudden death. Overall, up to 95% of all cardiac genetic disorders are inherited in an

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autosomal dominant fashion, meaning at-risk relatives have a 1 in 2 chance of inheriting the disease gene [5]. Consequently, both clinical and genetic screening is recommended in all families where a relative is found to carry a disease gene, so-called predictive or cascade testing, to determine who else in the family carries the gene and to facilitate the opportunity to initiate appropriate treatment and management.

CARDIAC ARRHYTHMIA SYNDROMES LINKING QT INTERVAL AND SIDS

Genetic cardiac arrhythmias were first proposed as a mechanism of SIDS in 1976 by a group in the United States who suggested a potential role of QT interval prolongation in SIDS cases [6]. LQTS is an inherited cardiac condition characterised by QT interval prolongation on the electrocardiogram (ECG) that may lead to lethal arrhythmias. [2] Several mutations in genes encoding cardiac ion channels have been correlated with the various forms of LQTS (LQTS1-13) and these have formed the basis of post-mortem genetic studies in SIDS cases [2,6–8].

In their landmark study from 1976, Maron et al. used electrocardiography (ECG) to study 42 sets of parents who had at least one infant die with a diagnosis of SIDS. They hypothesised that due to the inherited nature of the disease, if LQTS was to be implicated in SIDS, a proportion of parents with first hand experience of SIDS would also be affected by LQTS. Significantly, in the parents of infants who died from SIDS, one parent in each of ten parent pairs and two parents in one pair had prolongation of the QT interval on ECG. In a further key study by Schwartz et al. in 1998, SIDS cases over a 17-year period were studied, including correlation with recorded ECGs at birth [8]. Amongst 34,442 newborns, 24 deaths classified as SIDS occurred. Importantly, infants that died of SIDS had longer corrected QT intervals (QTc) than the surviving infants, suggesting a strong association between QT interval in the first week of life and SIDS. Collectively, these two key studies, coupled with other reported observations, provided the basis for the possibility that prolongation of the QT interval may predispose some babies to the development of SIDS. Furthermore, that genetic heart diseases which primarily affect the cardiac conduction system may be an underlying cause of SIDS in some cases.

CARDIAC ION CHANNELOPATHIES AND SIDS

Familial Long QT syndrome (LQTS)

Following the clinical studies that linked QT interval changes with SIDS cases, numerous studies have subsequently examined the role of cardiac ion channel gene mutations in SIDS cases, primarily those impacting the sodium ion channel SCN5A. Cardiac ion channels play a pivotal role in cardiac excitability and conduction of the cardiac impulse [9], i.e., the cardiac action potential and electrophysiology of the heart [10]. Consequently, mutations in cardiac ion channel genes can lead to disruptions in the electrophysiology of the heart and irregular cardiac rhythms resulting in sudden cardiac death. Figure 1 shows the relationship between genotype and molecular, cellular, organ and clinical phenotype in the arrhythmogenic pathogenetic pathway for SIDS. In addition, the potential for environmental factors to interact with the genetic factors is shown with acidosis, autonomics and sleep position potentially playing a part at certain stages [11].

Many studies and case reports over the last two decades have supported the potential role of cardiac genetic abnormalities in SIDS cases. Schwartz et al. described an important case regarding a baby who had a near-miss SIDS event and his parents [1]. The infant was found by his parents in a cyanotic, apnoeic, pulseless state and was subsequently taken to hospital and found to have ventricular fibrillation (ECG trace shown in Figure 2). The infant was restored to sinus rhythm and marked prolongation of the QT interval was documented (QTc = 648msec). Following treatment for LQTS, the infant was monitored and five years later remained free of symptoms. Genetic testing in the infant uncovered a substitution mutation in exon 16 of the coding sequence of the *SCN5A* gene, one of the sodium channel genes associated with familial LQTS and also BrS. Neither parent was found to carry the mutation, suggesting the mutation in the baby was a *de novo* event.

This case is one of several providing evidence for a cardiac origin in some SIDS cases. In this instance, as a near-miss case, the authors had to opportunity to perform an ECG post-event and determine the presence of a prolonged QT interval. In actual SIDS cases this is unfortunately not possible and in the absence of a prolonged QT interval or genetic mutation in the parents, the cause of death remains unknown. A further paper by Schwartz et al. described a

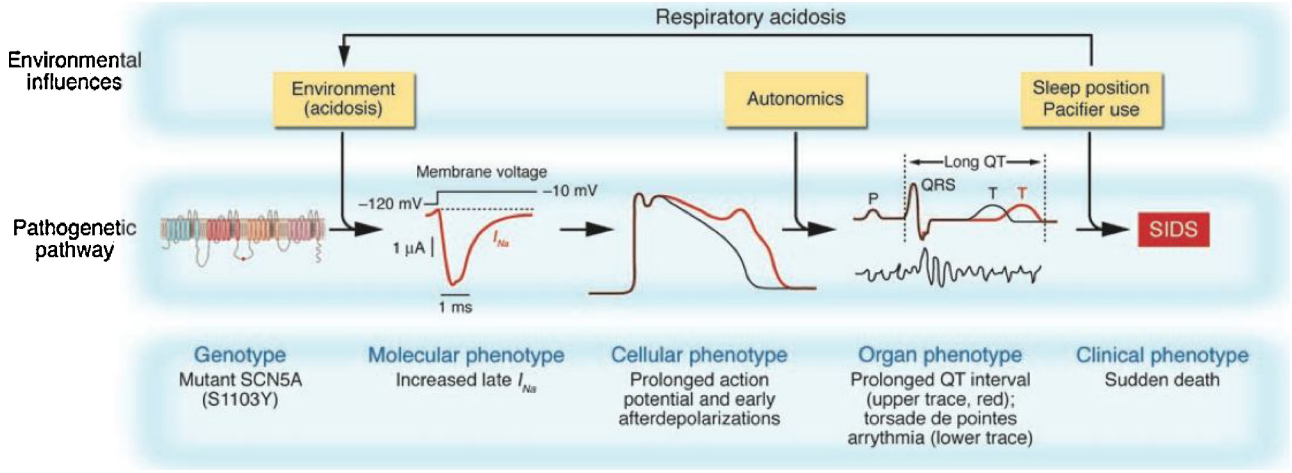

Figure 1. An arrhythmogenic pathogenetic pathway for SIDS: from genotype to phenotype. The genetic abnormality, a polymorphism in the cardiac Na^+ channel SCN5A, causes a molecular phenotype of increased late Na^+ current (I_{Na}) under the influence of environmental factors such as acidosis. Interacting with other ion currents that may themselves be altered by genetic and environmental factors, the late Na^+ current causes a cellular phenotype of prolonged action potential duration as well as early after depolarizations. Prolonged action potential in the cells of the ventricular myocardium and further interaction with environmental factors such as autonomic innervation, which in turn may be affected by genetic factors, produce a tissue/organ phenotype of a prolonged QT interval on the ECG and torsade de pointes arrhythmia in the whole heart. If this is sustained or degenerates to ventricular fibrillation, the clinical phenotype of SIDS results. (Adapted from Makielski et al. [11])