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Sudden infant death syndrome and long QT syndrome: The Zealots versus the Naysayers

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"Fools rush in where angels fear to tread."

- Alexander Pope, Essay on Criticism, 1711

Sudden infant death syndrome (SIDS), a leading cause of infant death, have a disproportionate psychosocial and medicolegal impact because they usually occur in otherwise healthy babies. While many pathophysiologic mechanisms for SIDS have been proposed, including respiratory dysfunction, cardiac dysrhythmias, cardiorespiratory instability, and inborn errors of metabolism, none has caused as much controversy as the cardiac dysrhythmia hypothesis. The existence of an association between SIDS and the long QT syndrome (LQTS) has been at the heart of this debate for over 30 years. In this issue of *Heart Rhythm*, Cronk et al report the first molecular and functional evidence to implicate *CAV3* as a pathogenic basis of SIDS [1]; how does this elegant study fit into the controversy?

What is SIDS?

The definition of SIDS originally appeared in 1969, but as a result of research in the field, was redefined as the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history [2]. There has been a major decrease in the incidence of SIDS coincident with the American Academy of Pediatrics (AAP) release of recommendations in 1992 that infants be placed down for sleep in a nonprone position [3]. However, despite marked reductions in rates over the past decade, SIDS is still responsible for more infant deaths in the United States than any other cause of death during infancy beyond the neonatal period [4].

What is LQTS?

LQTS is a heterogeneous disorder characterized by prolongation of the QT interval, multiform ventricular tachycardia (torsades de pointes), seizures, syncope, and sudden death; a positive family history of similar findings considerably aids the diagnosis. Of genes known to cause LQTS, 3 ion channels (*KCNQ1* (LQTS1, ~45%), *KCNH2* (LQTS2, ~45%), and *SCN5A* (LQTS3, ~10%) are the most common. Mutations in *ANK2* represent a nonchannel form of LQTS; mutations in *CAV3* represent a second example [5]. Despite a designation as

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"congenital", the average age at LQTS diagnosis is 30 years [6]. Diagnosis in the first year of life occurs in only ~4% of cases; neonatal LQTS is due to mutations in the 3 ion channels commonly associated with LQTS but has severe morbidity and mortality compared to LQTS in older patients [7-11]. In neonatal LQTS, compound heterozygous mutations, known to be associated with more severe LQTS phenotypes [12], are often noted.

LQTS and SIDS

While recognized risk factors suggest that SIDS is a heterogeneous entity with multifactorial pathogenesis, the LQTS hypothesis [13,14] has continued to garner support in the cardiovascular field due to reports of prolongation of the QT interval in SIDS cases [15,16] and identification of mutations in the same ion channel genes that cause LQTS in SIDS postmortem genetic samples [17-21]. The epidemiologic significance of these findings is the subject of ongoing debate [22,23].

Caveolins

As reviewed in the paper by Cronk et al [1], the caveolin genes (*CAV1*, *CAV*2 and *CAV3*), encode a family of cytoplasmic membrane-anchored scaffolding proteins that help to sculpt caveolae from the plasma membrane. The identification of signaling molecules within caveolae interacting with caveolins suggests a participation of caveolins in transmembrane signaling within caveolae microdomains. Both in vitro and in vivo studies have implicated caveolins in the pathogenesis of cancer, atherosclerosis and vasculoproliferative diseases, cardiac hypertrophy and heart failure, muscular dystrophies and diabetes mellitus [24-26]. Mutations in *CAV3* are now known to lead directly to a type of human limb-girdle muscular dystrophy [27-29] and LQTS [5].

CAV3 and SIDS

Based on the association of *CAV3* mutations with LQTS and the association of LQTS with SIDS, Cronk et al [1] used *CAV3* as a candidate gene for postmortem genetic testing in a population-based cohort of unrelated cases of SIDS (N = 134, average age = 2.7 months). CAV3 mutations (V14L, T78M, and L79R) were identified in 3/50 black infants, while no mutations were detected in 83 white infants (p value < 0.05). Biophysical studies showed that all 3 *CAV3* mutations caused an increase in late sodium (SCN5A) current, thereby mimicking the LQT3-like phenotype due to increased late sodium current. The functional deficits of the *CAV3* mutations were similar to those found in LQTS [5], in fact, one mutant, T78M, was reported in both studies. This is an important finding given the marked differences in characteristics of the mutant gene carriers in the LQTS group (average age ~21 years, 5 white and 1 black) versus the SIDS group (average age = 2.7 months, 0 white and 3 black).

So, does LQTS cause SIDS and what do we do about it?

The quote - "Fools rush in where angels fear to tread" - from Pope's Essay on Criticism seems particularly apt when addressing these two questions. In the Essay, Pope describes the antithesis of the ideal critic. We will resist the temptation to "rush in" to the SIDS-LQTS controversy in any great detail, since we are limited both by space and a realization that a glib review will not be able to grasp all the complexities and facets of this emotive issue.

Since the 1998 report by Schwartz et al [15], these two questions have become hot-button issues (in politician speak). As regards to the first question, it seems appropriate to review whether LQTS causes SIDS by referring to a landmark epidemiology paper. In 1965, Sir Austin Bradford Hill outlined a systematic approach for using scientific judgment to infer causation from associations [30]. He listed nine issues to be considered when judging whether an

observed association is in fact causal: 1) strength of association; 2) consistency of association; 3) specificity of association; 4) temporal sequence; 5) biological gradient (dose-response relationship); 6) biological plausibility; 7) coherence with existing knowledge; 8) experimental evidence; and 9) analogy. Review of the literature shows that SIDS-LQTS investigators have been successful in satisfying a number of these criteria. The paper by Cronk et al provides further evidence of biological plausibility in the LQTS-SIDS association [1].

The question as to whether newborns should receive screening to identify a risk of SIDS has been recently debated in this journal [16,22]. The cost-effectiveness of a screening program, the issue of false-positive ECG's and false-negative molecular testing were evaluated. Credible arguments for and against a screening strategy were clearly outlined. The two concluding remarks illustrate the conundrum: "... physicians -especially neonatologists and pediatricians -now have the duty and responsibility to inform the parents of a newborn about these possibilities. Failure to notify them of this small but definite risk is likely to carry medicolegal implications" [16]; and "Equally disturbing is the current lack of evidence on the effectiveness of preventive measures in all infants" [22]. Clearly, the debate has become somewhat circular, with little sign of reconciliation. In hindsight, perhaps the "zealots" were too enthusiastic and premature when they trumpeted that "LQTS causes SIDS", and conversely the "naysayers" may have been guilty of remaining too grounded in the epidemiological principles of screening interventions. Regardless of this fact, some consensus needs to be reached on this issue, out of respect for the patients we care for. In his concluding remarks, Sir Austin Bradford Hill states "All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time [30]." We propose the formation of a Task Force composed of responsible parties to tackle the LQTS-SIDS issue in the United States. Clearly, the time has come for this issue to be, if not laid to rest, at least "tucked in."

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