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EDITORIAL COMMENT

Can a Message From the Dead Save Lives?*

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Independently of cause, death of the young is always a tragedy for those left behind. When a young person's death is also sudden and unexplained, the tragedy is compounded and often unbearable. Although relatively infrequent, between 10% and possibly 30% of sudden deaths in the young remain unexplained after a thorough autopsy (1). Those autopsy-negative deaths occurring after the first year of life are often referred to as sudden unexplained death (SUD) syndrome. This definition distinguishes them from sudden deaths occurring in the first year of life, defined as sudden infant death syndrome (SIDS).

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For the medical profession, both SUD and SIDS are major challenges. For the parents and siblings of the victims, they represent devastating events that in most cases leave an indelible mark. When sudden death claims a child, an adolescent, or a young adult, parents and siblings may search desperately for years or a lifetime for " the truth" regarding what took their son or daughter. Whatever they come to accept as causal, needs to be associated with a mechanism they can understand. When the victims are infants, the same pattern is complicated by feelings of guilt, usually without basis or remedy, especially for the mothers (2).

Absence of structural cardiovascular abnormalities at autopsy logically suggests a functional disorder, most likely one capable of inducing a lethal arrhythmia. Two recent studies (3,4), based on cardiologic and clinical evaluations of family members of SUD victims, concluded that between 22% and 28% of cases respectively had evidence of inherited cardiac diseases or of channelopathies (usually long QT syndrome [LQTS], but also catecholaminergic ventricular tachycardia [CPVT]). This information has provided the rationale for seeking postmortem molecular evidence for a life-threatening familial disorder in SUD victims.

In this issue of the *Journal*, Tester and Ackerman (5) present compelling data implicating a cardiac channelopathy as the pathogenic basis for 35% of SUDs, with 20% of mutations related to LQTS. They had previously reported from the same series that 15% of cases had mutations related to CPVT1 (6). The present study involved 49 cases of SUD. The average age at death was 14 years. Molecular screening, performed on DNA extracted from either autopsy blood or frozen tissue, examined the 5 genes traditionally associated with LQTS (*KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2*), the gene for the Tawil-Andersen syndrome (*KCNJ2*) incorrectly labeled LQT7 by some investigators as discussed elsewhere (7), part of the gene *ANK2* implicated in a complex disease improperly called LQT4, and the specific mutation on the gene *CACNA1C* responsible for the Timothy syndrome, also called LQT8 (8). The LQTS mutations were found in 10 SUD cases (20%). Most of these mutations are associated with the clinical variant LQT1, the remaining with the variants LQT2 and LQT3. Two of the 10 are functional polymorphisms known to confer arrhythmic risk to a vulnerable host.

Importantly, personal and family history data were available for 9 of these 10 SUD cases with genetic mechanisms implicating LQTS. In 6 of these cases (67%), sudden death was the initial event; there were no harbingers. In the remaining 3 cases there was a personal history of either syncope or seizures. In addition, 5 of the 9 cases (56%) had a positive family history for cardiac events. Furthermore, the investigators were able to perform confirmatory genetic testing in relatives of 7 of these 9 cases. It is of considerable clinical significance that mutation carriers were identified in all (100%) of these families, for a current total of 23 subjects.

The present study represents one more contribution by Tester and Ackerman (5) to the field of sudden cardiac death and its genetic background. In conjunction with their prior publication (6), they have provided evidence that at least one-third of sudden and unexplained deaths in the young have a genetic origin attributable to 2 life-threatening conditions, LQTS and CPVT. Their merit lies in having conducted a methodologically careful study and in not having ignored the implications of their results.

This molecular investigation of SUD is the logical counterpart of the work carried out by Tester and Ackerman and by other investigators in SIDS, another condition in which the common denominator is a negative autopsy. It is now recognized that the origin of SIDS is multifactorial, i.e., that several different causes can lead to the sudden and unexpected death of an infant. Thirty years ago we (9) had proposed that among these several causes one of potential importance might have been LQTS. The implication was that the LQTS-related deaths might have been preventable, thus reducing the total burden of infant deaths grouped under the SIDS umbrella. This hypothesis led to several

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studies, ranging from epidemiology in a large cohort of infants studied prospectively with an electrocardiogram (ECG) (10) to proof-of-concept molecular identification of LQTS-causing mutations in victims of SIDS (11) or infants who survived a classic near-miss episode with documented ventricular fibrillation (12). All of these data contributed to the converging clinical and molecular evidence showing that at least anecdotal cases of SIDS were indeed caused by LQTS. This was followed by 2 cohort studies in SIDS victims. The first, by the present investigators, who reported LQTS-causing mutations in 5.2% of 58 white SIDS victims, and in 2.9% of 34 black SIDS victims (LQTS seems to be more rare among black patients) (13,14). A second study, in a cohort of 201 Norwegian SIDS victims, identified functional mutations in LQTS-related genes in 9.5% (95% confidence interval 5.8 to 14.4) of SIDS victims (15). The bottom line is that 30 years after the original hypothesis, there is now undeniable evidence that approximately 10% of SIDS victims carry LQTS-related mutations. The inescapable implication is that these arrhythmic deaths are preventable if early identification of the infants at risk is facilitated.

Extending these concepts to the prenatal period, there is growing evidence that a fraction—still to be quantified—of late stillbirths may result from the same mechanism, namely LQTS-related deaths (16–18). These diagnoses would be helpful for genetic counseling with the goal of reducing the probability of additional pregnancies with affected offspring. Preliminary and still unpublished data suggest that especially SCN5A mutations may contribute to late stillbirths.

What are the logical implications of the study by Tester and Ackerman (5)? Two are rather straightforward, and one requires a more thorough appraisal. Wisely, they have all been mentioned by the investigators, perhaps a bit too cautiously.

The first is that these findings should lead to changes in the management of SUD cases. Given the observation that one-third of these cases are of genetic origin, it seems no longer justifiable to ignore genotyping in these victims of sudden death. To find a disease-causing mutation will enable a rapid screening of all relatives; this should identify those who carry the same mutation as the victim. This approach should now become part of the routine postmortem study of SUD cases. The second and closely related implication is the utility and in fact necessity of performing a comprehensive cardiologic evaluation of first-degree relatives. The recognized limitation here is the possibility of incomplete penetrance expressed in these diseases (19).

The third implication is not only the most promising and rational, but also the most controversial. It concerns the institution of a far-flung program of ECG screening. Such a program, originally proposed on the basis of the first solid evidence linking QT prolongation and risk of SIDS (10), deserves careful analysis. The main objective of ECG screening would be the early identification of individuals affected by LQTS. Because the most severe cases of LQTS tend to have markedly prolonged QT intervals, their identification would be rather simple.

It seems appropriate to examine first the potential benefits of such a screening and then its feasibility and cost. The identification of still-asymptomatic individuals affected by LQTS would allow the early institution of beta-blocker therapy and the prevention of most life-threatening arrhythmic events. As noted also by Tester and Ackerman (5), a large percentage of sudden deaths among LQTS patients is not preceded by warning events. The ECG screening of family members will identify other affected family members with QT prolongation, and genotyping of the proband (with the current rate of success, 70%) would allow the recognition of "silent" mutation carriers within the extended families. When should this ECG screening be performed? Given the conclusive evidence that approximately 10% of SIDS cases are related to LQTS it seems logical, as suggested by the Task Force of the European Society of Cardiology (20), to screen in the third and fourth weeks of life. The objective of the screening would not be the prevention of SIDS, which would be unreasonable based on its low prevalence combined with its multifactorial origin, but the prevention of LQTS-related deaths, which include some occurring in the first few months of life and many more occurring in childhood and later on in life, especially younger than age 30 years as in the population of SUD victims studied by Tester and Ackerman (5).

We have just completed a prospective ECG study on 45,000 infants (21) that has shown both the complete acceptance by the families and the possibility of identifying not only asymptomatic infants affected by LQTS but also affected family members. Importantly, among those with a QTc >470 ms, which accounts for 7 of 1,000 of the entire population, genotyping has identified LQTS mutations in 50%. Furthermore, a few but significant cases of life-threatening congenital heart diseases—coarctation of the aorta and anomalous origin of the left coronary artery—that had escaped the initial medical visits were identified by the medical investigations prompted by ECG abnormalities and could be corrected by angioplasty or surgery before irreversible damage or death.

A cost-effective analysis based on Italy, which has 550,000 live births per year, has shown that the cost per year-of-life saved by an ECG screening program limited to the identification of infants affected by LQTS would be very low, approximately €11,000 (22).

When all of these considerations are taken into account, it should become evident that the study by Tester and Ackerman provides the important message that postmortem molecular screening is useful per se and also because it throws new light on feasible ways to reduce avoidable sudden deaths in the young.

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