Familial cardiological and targeted genetic evaluation: Low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes

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BACKGROUND It has been reported that cardiological screening and genetic evaluation in relatives of families with sudden unexplained death syndrome and unexplained cardiac arrest (UCA) may uncover a heritable etiology in a significant proportion of families.

OBJECTIVE To evaluate the yield of a comprehensive evaluation protocol of a large unselected cohort of consecutive families with *autopsy-negative* sudden unexplained death syndrome (termed sudden arrhythmic death syndrome [SADS]) and UCA.

METHODS We studied (1) 109 consecutive families (411 relatives) referred with 1 or more sudden deaths in the family and (2) 52 consecutive probands with UCA (91 relatives) referred by cardiologists between January 2007 and December 2012. A comprehensive cardiological screening was performed followed by targeted genetic evaluation if a clinical phenotype was proven or suspected. Diagnosis was made by a multidisciplinary team using published clinical criteria.

RESULTS A diagnosis was made in 19 of 109 families with SADS (yield 18%), with the majority having long QT syndrome (LQTS). Diagnosis varied according to proband age, with LQTS most common in the very young ($\leq$20 years) and Brugada syndrome in the older age probands ($\geq$40 years) ($P = .03$). In contrast, a diagnosis was made in 32 of 52 families with UCA (yield 62%), the majority of which had LQTS and Brugada syndrome. No clinical or circumstantial factors increased the likelihood of diagnosis in families with either SADS or UCA.

CONCLUSIONS In contrast to previously published series, a comprehensive strategy of cardiological evaluation and targeted genetic testing in more than 100 families with SADS was found to have a lower diagnostic yield (18%). Diagnostic yield in families with UCA was approximately 4 times higher (62%), which is consistent with the published literature.

KEYWORDS Sudden arrhythmic death syndrome; Sudden unexplained death syndrome; Unexplained cardiac arrest; Long QT syndrome; Brugada syndrome; Cardiological screening; Genetic testing

ABBREVIATIONS **ARVC** = arrhythmogenic right ventricular cardiomyopathy; **BrS** = Brugada syndrome; **CPVT** = catecholaminergic polymorphic ventricular tachycardia; **ECG** = electrocardiography/electrocardiogram; **ER** = early repolarization; **EST** = exercise stress test; **HCM** = hypertrophic cardiomyopathy; **LQTS** = long QT syndrome; **MRI** = magnetic resonance imaging; **SADS** = sudden arrhythmic death syndrome; **SQT** = short QT syndrome; **SUDS** = sudden unexplained death syndrome; **UCA** = unexplained cardiac arrest

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Introduction

Autopsy studies of young individuals who have had sudden death have shown that although a structural cardiac cause is present in up to 72% of the patients,[1] the cause of the fatal event remains unexplained in a significant proportion (6%–35%) of the patients, termed sudden unexplained death syndrome (SUDS).[1–5] Molecular autopsy of the deceased,[6–10] and cardiological and genetic examination of surviving relatives,[11–16] may uncover a heritable cardiac cause in up to 53% of these families. Collective evidence from these studies in addition to epidemiological data supports systematic cardiological screening and genetic evaluation of surviving relatives who may be at heightened risk for sudden death,[17] thus providing an opportunity for appropriate lifesaving intervention.[1,15,18] However, when

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these studies are individually evaluated, some studies have a sample size and there is significant variability in the reported yield of screening (ranging from 16% to 53%).[11–16,19,20] Thus, the generalizability of these results to broader patient populations is unclear. Importantly, not all probands included within these studies had autopsies performed.[12,13] Given that the causes of unexplained cardiac arrest (UCA) are likely to be similar to those of SUDS, this cohort may provide an ideal comparison for an achievable yield.[21,22] This study sought to evaluate the yield of a comprehensive protocol of cardiological screening and targeted genetic evaluation of a large unselected cohort of consecutive families with *autopsy-negative* SUDS (termed sudden arrhythmic death syndrome [SADS])[5] and UCA over a 6-year period.

Methods

This study was a retrospective review of consecutive families referred either to the cardiac genetics clinic or their affiliated cardiologists (J.K.V. and J.M.K.) at the Royal Melbourne Hospital between January 2007 and December 2012. The study was approved as a clinical practice audit by the Melbourne Health Human Research Ethics Committee.

Definitions

Sudden arrhythmic death syndrome

For this analysis, SADS was defined as a sudden unexpected death in an individual with no known history of cardiac disease in whom death occurred within 1 hour of symptom onset or within 24 hours of the individual being seen alive and well and in whom a full postmortem examination including toxicological investigations could not identify the cause of death.[1,13,19] The following families were excluded from the present analysis: (1) families in which autopsy revealed a structural cause of death such as arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, myocarditis, coronary artery disease, or valvular heart disease; (2) families in which autopsy revealed a noncardiac cause of death such as pulmonary embolus, cerebral hemorrhage, or drug overdose; (3) families with an existing diagnosis of an inheritable cardiac disease; (4) families whose probands were younger than 1 year.

Unexplained cardiac arrest

UCA was defined as occurring in a previously healthy individual with no known history of inherited cardiac disease with abrupt, unexpected, loss of consciousness occurring out of hospital with loss of vital signs within 1 hour of symptom onset, where resuscitation efforts were successful.[5,13,23,24] Patients were excluded from the present analysis if they had (1) an identifiable noncardiac etiology, (2) any evidence of coronary artery disease on electrocardiography (ECG) or coronary angiography, and (3) abnormal ventricular function or valvular heart disease.

Study population

Families with SADS

This study included families with 1 or more sudden deaths in a first-degree relative (parent, sibling, or child) referred by either the Victorian Institute of Forensic Medicine (representing the coroner) or a cardiologist. We offered assessment and appropriate screening to all available first- and second-degree relatives using cardiological and targeted genetic evaluation.

Families with UCA

This study included all probands with UCA and their families referred by hospital or an outpatient cardiologist.

Screening protocol

Families with SADS and UCA were assessed by a multidisciplinary team that included a cardiologist with specialist interest in structural heart disease, a cardiac electrophysiologist, clinical geneticists, genetic counselors, and cardiac genetic nurse, as well as input from the forensic pathologist and specialized genetics laboratory.[25] Molecular testing was performed in accredited diagnostic laboratories.

All probands with SADS and UCA and their families underwent a systematic protocol of screening (Figures 1 and 2). In families with SADS, the assessment of first- and second-degree relatives was performed in order to indirectly try to attribute the underlying cause of death in the proband. In families with UCA, the proband was directly evaluated and familial evaluation was performed if an inheritable etiology was confirmed or suspected.

The assessment began with (1) a detailed review of proband autopsy report, (2) an interview of family members about the circumstances of the proband's death, with a detailed review of the proband's medical history (including history of cardiac symptoms in life) and medication history,

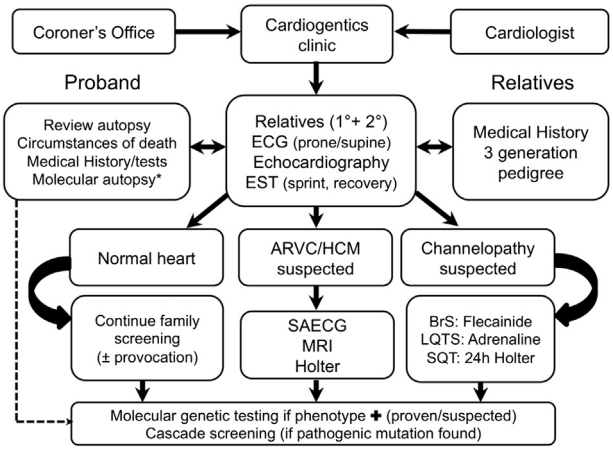

Figure 1 Protocol of assessment in families with SADS. Note that the assessment began with first- and second-degree relatives to look for potential causes of death of probands. 1° = first degree; 2° = second degree; ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; ECG = electrocardiogram; EST = exercise stress test; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; MRI = magnetic resonance imaging; SAECG = signal averaged electrocardiogram; SQT = short QT syndrome.