REVIEW ARTICLE

The role of genetic testing in unexplained sudden death

Q20 **CHRIS J. MILES, and ELIJAH R. BEHR**

LONDON, UK

Most sudden deaths are because of a cardiac etiology and are termed sudden cardiac death (SCD). In younger individuals coronary artery disease is less prevalent and cardiac genetic disorders are more common.[1] If sudden death is unexplained despite an appropriate autopsy and toxicologic assessment the term sudden arrhythmic death syndrome (SADS) may be used.[2] This is an umbrella term and common underlying etiologies are primary arrhythmia syndromes with a familial basis such as Brugada syndrome, long QT syndrome, and subtle forms of cardiomyopathy. The first clinical presentation of these conditions is often SCD, which makes identification, screening, and risk stratification crucial to avert further deaths. This review will focus on genetic testing in the context of family screening. It will address the role of the "molecular autopsy" alongside current postmortem practices in the evaluation of SADS deaths. We describe the current data underlying genetic testing in these conditions, explore the potential for next-generation sequencing, and discuss the inherent diagnostic problems in determination of pathogenicity. (Translational Research 2015;■:1–15)

Abbreviations: AHA = American Heart Association; APHRS = Asia Pacific Heart Rhythm Society; ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; ChIP = channel interacting protein; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; EHRA = European Heart Rhythm Association; ERS = early repolarization syndrome; HCM = hypertrophic cardiomyopathy; HRS = Heart Rhythm Society; IVF = idiopathic ventricular fibrillation; LQTS = long QT syndrome; ONS = Office for National Statistics; PCCD = premature cardiac conduction disease; SADS = sudden arrhythmic death syndrome; SCD = sudden cardiac death; SNR = signal-to-noise ratio; SQTS = short QT syndrome; SUDS = sudden unexpected death syndrome; VUS = variant of unknown significance

INTRODUCTION

The estimated incidence of sudden cardiac death (SCD) in the general population in Europe and the United States (US) is between 50 and 100 per 100,000 per annum.[3-5] SCD claims 300,000–400,000 deaths per annum in the US[6,7] and there were an estimated 70,000 SCDs in the UK in 2010, most because of ischemic events.[8] SCD is usually defined as an unheralded witnessed instantaneous death but it may also be described as being preceded by a prodrome of acute cardiac symptoms up to 1 hour before death.[7] Unwitnessed cases without a prior deterioration in the preceding 12–24 hours may also be included. Estimates vary, however, because of a dependence on the presence

From the Division of Clinical Sciences, Cardiovascular Sciences Research Centre, St George's University of London, London, UK.

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Reprint requests: Elijah R. Behr, Division of Clinical Sciences, Cardiovascular Sciences Research Centre, St George's University of London, Cranmer Terrace, London SW17 0RE, UK; e-mail: ebehr@sgul.ac.uk.

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of autopsied vs nonautopsied cases and the variability of definitions and the duration of prodromal symptoms before the terminal event. A national prospective survey of English coroners' cases for more than a 20-month period in the late 1990s evaluated sudden deaths in Caucasians aged 4–64 years with no history of cardiac disease, negative toxicology, and last seen alive within 12 hours of death.[2] A normal coroner's autopsy and subsequent evaluation of the heart by a cardiac pathologist established these as sudden arrhythmic death syndrome (SADS) cases with an estimated incidence of up to 1.38 per 100,000 per annum.

SCD in the young. In individuals aged <35 years inherited cardiac diseases are more prevalent and estimates of the incidence of SCD vary depending on definitions and study site. For example, a Danish nationwide analysis of deaths from 2000 to 2006 revealed an annual incidence of young SCD of 2.8 per 100,000,[9] whereas a retrospective US study of >6 million military recruits reported an incidence as high as 13 per 100,000 per annum.[10] Puranik et al[11] retrospectively reviewed pathologic reports from 427 autopsied sudden death cases aged 5–35 years at a forensic medical facility from 1995 to 2004 in Sydney. The most common cardiac cause of death was presumed arrhythmia in those with no (or minimal) structural heart disease (29%), that is, SADS. Retrospective analysis of death certification, autopsy reports, and registry data estimated that 31% of autopsied SCD cases in Danes aged 1–49 years were unexplained and attributed to SADS.[12]

Conversely, in 79% of 197 cases of young SCD in Italy, histologic analysis yielded a structural diagnosis such as cardiomyopathy or focal myocarditis; 6% were unexplained and attributable to SADS.[13] In the Veneto region of Italy, studies have implicated arrhythmogenic right ventricular cardiomyopathy (ARVC) in 20% of sudden deaths among athletes and the young.[14] Maron et al[15] described sudden deaths in young competitive athletes for more than a 27-year period in the US: 56% were because of cardiovascular disease, the most common cause (36%) being hypertrophic cardiomyopathy (HCM).

In the UK the incidence of cardiac death in the young (≤35 years) as determined by analysis of Office for National Statistics data was 1.8 per 100,000 in England and Wales (2002–2005). Critical appraisal estimated the incidence of SADS as 0.24 per 100,000 per annum, significantly higher than the 0.1 per 100,000 reported by the Office for National Statistics as instantaneous unexplained sudden death, but still less than most other estimates.[16] This is likely to be because of misclassification of the cause of death as mortality data are largely derived from death certificate documentation that may under-report the true incidence of cardiac arrhythmia. For example, in one study a significant proportion (23%) of unexplained drowning cases carried mutations associated with arrhythmia syndromes,[17] and certification of sudden death in epilepsy may overlook cases, which result from a primary arrhythmic cause.[18,19]

DEFINING SADS

A consensus statement from the Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), and the Asia Pacific HRS defines SADS as a pathologic diagnosis of exclusion after postmortem cardiac investigation and toxicologic analysis.[20] Even if nondiagnostic pathology is detected, cases should still be considered as SADS because of the high chance of underlying inherited ion channel disease.[21] Expert autopsy is also recommended as general pathologists may misdiagnose cases, over diagnosing ARVC, and under diagnosing SADS.[22] Guidelines for autopsy practice exist and include detailed description of postmortem sampling techniques with integration of specialist skills in the evaluation of possible familial disorders.[23,24] In the US, the state-wide Sudden Death in the Young Registry collates young SCD case data, using DNA analysis in a subset of cases for the purpose of further evaluation and future research.[25] Unfortunately, access to expert cardiac pathology is very much limited internationally.

DIAGNOSTIC APPROACHES AND GENETIC TESTING

Two approaches may be taken to make a diagnosis in a family: familial clinical evaluation with genetic testing targeted to phenotype and postmortem genetic testing "the molecular autopsy." The overall aim is to identify cardiac genetic disease were present and institute preventative treatment were necessary to avert further SCD.[26] The clinical role of genetic testing is therefore a diagnostic one and dependent on identifying mutations, that is, disease-causing or pathogenic rare genetic variants. The rapid development in sequencing technology has, however, led to the identification of frequent rare genetic variation in both healthy and affected individuals. Rare variants are often private to a specific family and therefore may be unknown in the literature. Their associated risk for disease causation and therefore their clinical significance is often uncertain and a major challenge as incorrect inferences of causality can have serious implications for diagnosis and management of families. If pathogenicity of a rare variant remains uncertain then it is termed a "variant of unknown significance" (VUS).[27]