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Review

Investigation of the family of sudden cardiac death victims

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ABSTRACT

Sudden cardiac death in the young is a devastating event and a significant proportion of cases are caused by an underlying inherited cardiac condition. This justifies investigation of surviving blood relatives in order to identify a definite diagnosis and to prevent further deaths. First-degree relatives, obligate carriers, and symptomatic relatives are family members who are more likely to be affected and/or at risk and should be prioritized for evaluation. Cardiological clinical evaluation of family members is staged, less invasive investigations being first offered and more invasive tests being subsequently considered if a diagnosis is not made. If a phenotype is identified, then targeted genetic testing can be undertaken. Results of post-mortem genetic testing (the molecular autopsy) in the decedent may confirm familial results or guide cascade testing in order to identify presymptomatic individuals. When a genetic diagnosis is made in the sudden death case, initial familial genetic testing should focus on the parents to determine whether the mutation is inherited, or arose *de novo* in the deceased. Management of the surviving family and genetic counselling should be offered in the setting of a specialized, multidisciplinary cardiac genetic team to offer the most accurate care and support to family members. Further research into understanding the genetic basis of sudden cardiac death and new diagnostic modalities will contribute to improve management and prevention of sudden cardiac death in the young.

1. Introduction

Sudden cardiac death (SCD) in the young carries devastating consequences for both the surviving family and the community. Unexplained sudden death (Sudden unexplained death syndrome, SUDS) refers to a sudden cardiac death that occurs in an apparently healthy and often young individual within an hour of the onset of symptoms and for no apparent reason [1,2]. It is a diagnosis of exclusion that covers a number of possible etiologies. If the death remains unexplained despite thorough death scene investigation and comprehensive post-mortem examination, including histopathology and toxicology, the term sudden arrhythmic death syndrome or SADS is preferred [3,4]. The term sudden infant death syndrome or SIDS is used in cases under 1 year of age [5], although this diagnosis implies a more stringent circumstantial and forensic investigation [6]. There is also much less data around the role for clinical cardiological evaluation in SIDS.

Not only is the proportion of SADS apparently higher in the young, but victims are also more commonly young men who die suddenly in their sleep or at rest [4]. Indeed, an undiagnosed inherited cardiac condition is likely to explain a substantial subset of SADS in adult victims [7] as well as in infants and children [8]. Once a diagnosis of SADS has been made, further management tries to establish the exact cause of death in the deceased and involves investigation of surviving family members. The aim is to avoid additional deaths among relatives in case of an underlying inherited cardiac disorder.

Investigation of the surviving family is particularly relevant in cases of: (a) SUDS or SADS; (b) family history of premature sudden death; (c) or post-mortem examination suggesting an inherited structural cardiac disease such as a hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy [9].

This review article aims to provide a comprehensive up-to-date approach for evaluation and management of family members of young SUDS or SADS victims.

2. Background

2.1. Epidemiology of Unexplained Sudden Cardiac Death

Incidence and prevalence of SADS vary according to studies. In the United Kingdom, the incidence of SADS among the general population aged 4 to 64 years has been estimated to be up to 1.34/100,000 *per annum* [4] with 4.1% of sudden cardiac death in the age group 16 to 64 years being unexplained [10], whereas a 0.76/100,000 year incidence

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of SADS, accounting for 27% of the SCD in subjects aged 14 to 35 years old has been reported in an Irish study [11]. This is consistent with an Australian study performed in the 5 to 35-year-old age group [12].

The incidence of SIDS is well defined however and significantly exceeds the incidence of SADS in young adults or in children over 1 year of age. In the United States, a population-based study revealed an annual incidence of SIDS of 80/100,000 for children <1 year and of SADS of 3/100,000 for children age 1–4 years [13]. An Irish national study found similar results with a SIDS rate of 59/100,000 in children <1 year compared to as SADS rate of 1.4/100,000 among children aged 1–4 [14]. Risk reduction campaigns have resulted in an unequivocal decrease in incidence by 50–90% [15], most noticeably the 1990s 'Back to Sleep' campaign advocating a supine sleep position for infants. However, despite these efforts SIDS rate has plateaued and its current rate is 53/100,000 in the United States and 40/100,000 livebirths in the UK [16,17], positioning SIDS as the leading cause of post-neonatal infant mortality in developed countries [6,15].

2.2. Causes of Sudden Cardiac Death in the Young

Whereas coronary artery disease and myocardial infarction account for over 90% of cases of SCD in the general population [18] SCD in the young – namely below the age of 40 – is caused by a wide variety of causes that can be categorized into structural cardiac diseases and primary electrical disorders [19]. Structural causes of sudden cardiac death include: (a) inherited cardiomyopathies such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC) and left ventricular non-compaction; (b) congenital heart diseases; (c) acquired cardiac condition such as coronary artery disease or myocarditis [1]. These structural cardiac conditions are usually identified by postmortem examination, but subtle forms of the disease may not be recognized, even by expert pathologists. Primary electrical diseases typically occur in structurally normal hearts and are not recognized by postmortem examination. This includes congenital long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome and idiopathic ventricular fibrillation [20,21]. Causes of sudden death in the young are detailed elsewhere in this journal issue (Davis et al., same issue).

3. Management of Family Members

An algorithm to describe the investigative strategy of families of SCD victims is summarized in Fig. 1.

3.1. Rationale of the Autopsy

Postmortem pathological examination may identify an inherited structural heart disease, justifying familial investigations. An autopsy-negative case must lead to investigation of surviving relatives as well, as primary electrical disorders can cause SADS and may be familial. The accurate identification of the cause of sudden death is therefore crucial to determine whether an underlying genetic cardiac disorder is likely and whether there are other potentially at-risk family members. Expert autopsy is recommended as general pathologists may misdiagnose cases, overdiagnosing ARVC, and underdiagnosing 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].

3.2. Molecular Autopsy of the Victim (the Decedent)

Investigations in the family can depend on the results of postmortem genetic testing, or 'molecular autopsy', of the victim. Introduced >10 years ago [24], postmortem genetic testing in addition to comprehensive post-mortem examination has proven to be useful in identifying an underlying cause in unexplained SCD. Molecular autopsy of the victim involves the collection of tissue suitable for DNA extraction at autopsy and mutation analysis for selected candidate genes responsible for the main primary electrical disorders. Recent Heart Rhythm Society/European Heart Rhythm Association guidelines recommend the use of targeted postmortem genetic testing in SADS cases especially where clinical evidence suggests a diagnosis of LQTS or CPVT [9,25]. Collection of blood and/or suitable tissue for molecular autopsy is also recommended in case of SIDS as an arrhythmia syndrome focused postmortem genetic testing can be useful [9], although data are still limited. Initial studies targeted a limited number of candidate genes, focusing upon the common causes of LQTS (*KCNQ1*, *KCNH2*, *SCN5A*), BrS (SCN5A) and CPVT (*RyR2*) [26]. Recent advances in sequencing technologies (next-generation sequencing) have now made it possible to screen in detail an increasing number of genes in cardiac gene panels at relatively low cost and using a limited amount of DNA. In addition, whole-exome sequencing, where the coding regions of all ~22,000 genes are sequenced, has also been employed in post-mortem genetic testing [27]. It is important to note that these technologies extend to the inclusion of genes involved in the inherited cardiomyopathies in addition to the channelopathy genes [28,29]. Testing modalities and diagnostic yield of molecular autopsy are presented in details elsewhere in this issue of the journal (Semsarian et al., same issue).

3.3. Review of Family History

Evaluation of the surviving family of the SCD victim is performed with a full clinical history with detailed information spanning a minimum of three generations, including the deceased individual. Particular attention should be given to relatives who have suffered suspicious symptoms, such as syncope and seizures, as well as any family history of sudden death at a young age. If necessary, medical records, postmortem reports and death certificates should be reviewed to confirm any suspected diagnoses in relatives. Further information about the family history can often provide useful insight into the genetic heart disease affecting the family [3,30,31].

3.4. Clinical Evaluation

A standardized approach to clinical evaluation of first-degree relatives is important [1]. The strategy of evaluation of family members is staged, as recommended by the Heart Rhythm Society/European Heart Rhythm Association consensus statement for inherited arrhythmia syndromes [9]. These recommendations also apply to families of SIDS' victims although with less certainty of utility [9]. Less invasive investigations are first offered and more invasive tests are then considered if a diagnosis is not made. First-degree relatives, obligate carriers, and symptomatic relatives are more likely to be affected and/or at risk of SCD and should be prioritized for evaluation [31].

All relatives should have a comprehensive review of medical and family history, physical examination, resting ECG (with high intercostal space leads), exercise ECG, and a transthoracic echocardiogram. Depending on the clinical situation, further investigations may include 24 h ECG monitoring, signal-averaged ECG, pharmacological provocation tests (such as a sodium channel blocker challenge in suspected BrS patients) and cardiac magnetic resonance imaging (especially in suspected arrhythmogenic right ventricular cardiomyopathy) [1,31]. It should be noted that resting and exercise ECGs, cardiac imaging and sodium channel blocker challenge offer the most diagnostic value across studies [31–33]. If a diagnosis is made in a proband then genetic testing can be offered targeted to the phenotype [9].

Clinical evaluation alone in relatives of SCD victims may identify an underlying cause in around 30% (range: 13.2% to 52.6%) of selected and comprehensively evaluated families (Fig. 2), identifying an inherited arrhythmia syndrome (such as LQTS, CPVT or BrS) or a subtle form of inherited cardiomyopathy (such as HCM or ARVC) [3,26,29–36].

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