The pathological investigation of sudden cardiac death

Sudden cardiac death is unexpected death within 1 hour of symptoms. A total of 6 million cases of sudden death occur per year world wide with 50 000 in the UK and 300 000–400 000 in the USA (Mazeika, 2001; Anonymous, 2002). Cardiac causes account for 60–80% of cases (Myerburg et al, 1993). Most cases are the result of ischaemic heart disease (Bowker et al, 2003). Detecting those at risk is difficult since many will be asymptomatic and the first presentation may be sudden death.

Sudden cardiac death is the commonest and often the first manifestation of coronary heart disease (Reddy, 2002), but the increasing incidence of congestive cardiac failure also contributes to this increase (Anonymous, 1994). The greatest incidence occurs in cohorts with identifiable risk factors but most events – in absolute numbers – occur in individuals without prior known risk factors.

A UK study in 1988 was the first to highlight other causes of sudden cardiac death described as non-ischaemic in 7.5% of cases. In another 7% of cases, no cause of death was found (Thomas et al, 1988). A later prospective study in the 1990s found potentially inheritable cardiomyopathies in 5% of cases and in 7% the deaths were again totally unexplained despite detailed examination by cardiac pathologists (Bowker et al, 2003).

The term sudden cardiac death or sudden arrhythmic death syndrome was introduced and refers to the presumed mode of death as a lethal cardiac arrhythmia (Bowker et al, 2003). Non-ischaemic causes of sudden cardiac death are of major importance because they include genetic diseases, such as hypertrophic cardiomyopathy, dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy.

Most cases of sudden arrhythmic death syndrome are in young males with estimates of over 3000 deaths each year in the UK. Development of a national register with evaluation of families is important (Behr et al, 2007). Sudden arrhythmic death syndrome is gradually being accepted by pathologists, coroners and cardiologists and in the future hopefully will be accepted as an official cause of death by the Office of National Statistics.

The emergence of the molecular channelopathies such as long QT, short QT and Brugada syndrome giving rise to lethal cardiac arrhythmias in the last 15 years has transformed the importance of these unexplained cardiac deaths (Bowker et al, 2003). These channelopathies are inherited in an autosomal dominant manner. Molecular techniques are now applied (Ackerman, 2009) when limits of morphological diagnosis have been reached (de la Grandmaison, 2006; Ladich et al, 2006).

Diseases of the brain and heart account for the majority of deaths in developed countries. Yet the heart and brain remain very emotive organs for the public and underlie the reluctance of relatives to agree to their retention at autopsy (Hull et al, 2007). Pathologically, sudden cardiac death cases can be poorly investigated especially when the question of cardiomyopathy or cardiac hypertrophy arises (Ranson, 2007).

The National Service Framework Chapter 8, which emphasized the role of cardiac pathology in sudden cardiac death prevention, was published in March 2005. Since then there have been campaigns to heighten the central role that cardiac pathology plays in making a specific diagnosis and a research unit has been established sponsored by the charity Cardiac Risk in the Young (CRY; www.c-r-y.org.uk) to investigate these sudden cardiac deaths. The unit now acts as a referral centre where the coroner or pathologist will send the heart with the full consent of the relatives and a detailed examination and report is provided within 14 days. The initial results were published in 2006 (Fabre and Sheppard, 2006), as were the findings on sudden cardiac death in sport highlighting cardiac inherited conditions (de Noronha et al, 2009).

The cardiomyopathies, inflammatory myocardial diseases, anomalous coronary arteries and ion channelopathies are the most frequent causes of sudden cardiac death in the young. In up to 50% of families there is evidence of inherited cardiac electrical or muscle disease (Behr et al, 2008). Hypertrophic cardiomyopathy, arrhythmogenic ventricular cardiomyopathy and dilated cardiomyopathy are the most frequent conditions. Development of a prospectively validated risk-stratification algorithm for the cardiomyopathies remains an important clinical challenge. Histological blocks must include the full circumference of the left and right ventricles to come to a correct diagnosis (Fletcher et al, 2006). Idiopathic left ventricular hypertrophy may be related to death during exercise (Fabre and Sheppard, 2006; de Noronha et al, 2009). The aetiology of this remains to be determined.

In the CRY Centre for Cardiac Pathology's database of sudden cardiac death cases, 3.0% were associated with non-atherosclerotic coronary pathology including anomalous coronary arteries, coronary artery dissection, coronary artery vasculitis, coronary artery spasm, idiopathic arterial calcification of infancy and fibromuscular dysplasia (Hill and Sheppard, 2010).

Screening

Prevention is one of the leading challenges facing clinicians today. The advent of effective therapies, particularly implantable cardioverter defibrillators, has prompted calls for universal screening. Since prospective cardiac assessment of the general population is not feasible, the solution may be to target high-risk subgroups, namely patients with cardiac symptoms, relatives of sudden cardiac death victims, and competitive athletes.

The recommended preliminary work-up includes a 12-lead electrocardiogram, signal-averaged electrocardiogram, transthoracic echocardiogram, exercise test and ambulatory electrocardiogram monitor-

ing. Cardiovascular magnetic resonance is a useful adjunct. Provocative challenge with a sodium-channel blocker may be of value in unmasking the Brugada syndrome. Identification of disease-causing mutations in affected individuals may facilitate cascade screening of families (Tan et al, 2005; Sen-Chowdhry and McKenna, 2006). However, universal agreement regarding the most appropriate method for cardiovascular screening is lacking and complex issues regarding feasibility, false positive results, cost-effectiveness, and physician and health system infrastructure still remain regarding large-scale implementation of electrocardiogram screening.

Management

The implantable cardioverter defibrillator is the only reliable therapy in patients with Brugada syndrome and short QT syndrome. In long QT syndrome and catecholinergic polymorphic ventricular tachycardia, the primary therapy relies on beta-blockers. In all electrical diseases, risk stratification is based on the clinical phenotype, including the electrocardiogram, the history of unexplained or disease-related syncope, and sudden cardiac arrest. In long QT syndrome and catecholinergic polymorphic ventricular tachycardia, demographic data such as age and gender are important factors for risk stratification. The genotype contributes to risk stratification only in long QT syndrome and catecholinergic polymorphic ventricular tachycardia. Patients with cardiomyopathies and channelopathies have to be risk stratified individually.

Worldwide, less than 1% of those who experience sudden cardiac arrest survive (Pochmalicki et al, 2007). Widespread availability of automated external defibrillators and effective utilization of public access defibrillation programmes may improve management of out-of-hospital cardiac arrest (Sukhija et al, 2007).

Cardiac pathologists emphasize that the investigation of sudden death involves five steps:

1. The clinical features, especially the history and circumstances of death
2. Autopsy examination and histology
3. Further laboratory tests including toxicology
4. Formulation of a diagnosis
5. Recommendation for family screening by specialized cardiologists.

Conclusions

In order that the causes of sudden cardiac death can be readily identified, detailed case history, meticulous post-mortem examination and complete toxicological screening are essential to arrive at the specific diagnosis. Most cases of sudden death have a cardiac cause so detailed examination of the heart is essential in all cases. Many of these cardiac causes are genetic so communication with the family and appropriate cardiological screening are essential. BJHM

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KEY POINTS

- Sudden cardiac death occurs mainly in young males.
- We do not know the true incidence of this entity in the population.
- Most sudden cardiac death in the young are the result of inherited disease, either cardiomyopathy or channelopathy.
- Detailed examination of the heart with histology and toxicology is essential.
- Once a pathological diagnosis is made, the family will need expert cardiological screening.